Multiple Technology Appraisal

Natalizumab (originator and biosimilar) for treating highly active relapsing–remitting multiple sclerosis after disease-modifying therapy [ID6369]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Natalizumab (originator and biosimilar) for treating highly active relapsing–remitting multiple sclerosis after disease-modifying therapy [ID6369]

Contents:

The following documents are made available to stakeholders:

Access the **final scope, final stakeholder list** and **Research Protocol** on the NICE website.

1. **Company submissions** from:
   a. Biogen
   b. Sandoz
      i. Submission
      ii. Summary of Information for Patients (SIP)
      iii. Reference - access to natalizumab in England

2. **Patient groups, professional group and NHS organisation submissions** from:
   a. MS Society
   b. Association of British Neurologists

3. **Expert personal perspectives** from:
   a. Professor Ruth Dobson – clinical expert, nominated by Association of British Neurologists

4. **Assessment Report** prepared by the Bristol Technology Assessment Group
   a. Assessment report
   b. Updated External Assessment Group Report

5. **Consultee and commentator comments on the Assessment Report and model** from:
   a. Biogen
   b. Sandoz
   c. Association of British Neurologists
   d. Merck Serono
   e. Novartis Pharmaceuticals

6. **Updated Assessment Report in response to stakeholder comments from the Assessment Report and model consultation** from Bristol Technology Assessment Group
   a. EAG's response to consult comments
   b. External Assessment Group Addendum

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple technology appraisal

Multiple sclerosis (relapsing, remitting, highly active) – natalizumab and Tyruko (natalizumab biosimilar) (after disease modifying therapy) [ID6369]

Document B

Company evidence submission

August 2024

File name	Version	Contains confidential information	Date
ID6369_Tysabri_MTA_Highly-active-RRMS_Submission-dossier_v1.0_[redacted]	1.0	No	13 August 2024

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Abbreviations

ABN	Association of British Neurologists
AE	Adverse event
AHSCT	Autologous haematopoietic stem cell transplantation
ARR	Annualised relapse rate
CD20	Cluster of differentiate 20
CDI	Confirmed disability improvement
CDW	Confirmed disability worsening
CI	Confidence interval
CIS	Clinically isolated syndrome
CMO	Contract manufacturing organisation
CNS	Central nervous system
CSF	Cerebrospinal fluid
DMT	Disease-modifying therapy
DNA	Deoxyribonucleic acid
EDSS	Expanded Disability Status Scale
EID	Extended interval dosing
ELISA	Enzyme-linked immunosorbent assay
EQ-5D	Euroqol-5 Dimensions
GA	Glatiramer acetate
Gd+	Gadolinium-enhancing
HCP	Healthcare professional
HRQoL	Health-related quality of life
ISO	International Organization for Standardization
IV	Intravenous
JCV	John Cunningham virus
MHRA	Medicines and Healthcare products Regulatory Agency
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
PCR	Polymerase chain reaction
PML	Progressive multifocal leukoencephalopathy
PPMS	Primary progressive multiple sclerosis
Q4W	Every 4 weeks
Q6W	Every 6 weeks
Q8W	Every 8 weeks
Q12W	Every 12 weeks
RCT	Randomised controlled trial
RES	Rapidly evolving severe
RRMS	Relapsing–remitting multiple sclerosis

SAE	Serious adverse event
SC	Subcutaneous
SD	Standard deviation
SID	Standard interval dosing
SLR	Systematic literature review
SmPC	Summary of product characteristics
SPMS	Secondary progressive multiple sclerosis
TA	Technology appraisal
TOP	Tysabri Observational Program
UK	United Kingdom
US	United States

B.1 Decision problem, description of the technology and clinical care pathway

B.1.1 Decision problem

Natalizumab (Tysabri®) – referred to throughout this submission as natalizumab-TYS – is indicated as a single disease-modifying therapy (DMT) in adults with highly active relapsing–remitting multiple sclerosis (RRMS) for the following patient groups:[1, 2]

- Patients with highly active disease despite a full and adequate course of treatment with ≥1 DMT

  or

- Patients with rapidly evolving severe (RES) RRMS defined by two or more disabling relapses in one year, and with one or more Gadolinium-enhancing (Gd+) lesions on brain Magnetic Resonance Imaging (MRI) or a significant increase in T2 lesion load as compared to a previous recent MRI

The submission focuses on patients with highly active RRMS, specifically **patients with highly active disease despite a full and adequate course of treatment with ≥1 DMT** in alignment with the final scope. While this population also includes those patients with rapidly evolving severe highly active RRMS (RES RRMS), natalizumab-TYS is already recommended as a treatment option by the National Institute for Health and Care Excellence (NICE) for patients with RES RRMS (Technology Appraisal [TA]127). The RES RRMS subpopulation is not in scope for this TA.

A summary of the decision problem is shown in Table 1.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with highly active relapsing–remitting multiple sclerosis despite a full and adequate course of treatment with at least 1 disease-modifying therapy	Adults with highly active relapsing–remitting multiple sclerosis despite a full and adequate course of treatment with at least 1 disease-modifying therapy. The RES RRMS subpopulation is not in scope for this technology appraisal	Not applicable
Intervention	• Natalizumab (Tysabri®) • Natalizumab biosimilar (Tyruko®)	As per final scope	Not applicable
Comparator(s)	• Glatiramer acetate • Interferon β-1a • Interferon β-1b • Alemtuzumab • Cladribine • Fingolimod • Ocrelizumab (if alemtuzumab contraindicated or otherwise unsuitable) • Ofatumumab • Ponesimod • Autologous haematopoietic stem cell transplantation	• Ocrelizumab • Ofatumumab • Ponesimod • Cladribine	Glatiramer acetate, interferon β-1a and interferon β-1b are not considered relevant comparators to natalizumab-TYS. Although these low/moderate efficacy DMTs have been used historically as treatment options for patients with highly active relapsing–remitting multiple sclerosis they are now rarely used in clinical practice due to the current availability of high-efficacy DMTs (UK clinical opinion)[3–5] Fingolimod, alemtuzumab and autologous haematopoietic stem cell transplantation are not considered relevant comparators to natalizumab-TYS. [redacted]6

			Fingolimod use is expected to decline further in the future due to the requirement for CV and skin lesion monitoring (UK clinical opinion).[3–5] Autologous haematopoietic stem cell transplantation is used as a last-line therapy when high-efficacy DMT options have been exhausted (UK clinical opinion).[3–5] Autologous haematopoietic stem cell transplantation is only available in a small number of NHS centres and very few people with multiple sclerosis are accepted for treatment.[7, 8] Alemtuzumab is also considered as last-line therapy for the majority of patients when other DMT options have been exhausted (UK clinical opinion).[3, 5] Alemtuzumab is associated with serious adverse events, including thyroid disorders, immune thrombocytopenic purpura and kidney disease.[9]
Outcomes	• Relapse rate • Severity of relapse • Disability (for example, Expanded Disability Scale [EDSS]) • Disease progression • Symptoms of multiple sclerosis	• Relapse rate • Disability • Disease progression • Freedom of disease activity • Adverse effects of treatment • Mortality	Symptoms of multiple sclerosis were not specified outcomes in the systematic literature review/meta-analyses of non-RCT data in patients with highly active relapsing–remitting multiple sclerosis despite a full and adequate course of treatment with ≥1 DMT (Section

	• Freedom of disease activity (for example lesions on MRI scans) • Mortality • Adverse effects of treatment • Health-related quality of life	• Adverse effects of treatment	B.2.1 and B.2.7 or the TOP study (Section B.2.4.1).

Abbreviations: CV, cardiovascular; DMT, disease-modifying therapy; MRI, magnetic resonance imaging; Natalizumab-TYS, natalizumab (Tysabri®); NHS, National Health Service; RES, rapidly evolving severe; TOP, Tysabri® Observational Program

SUMMARY

Biogen have taken a pragmatic approach to this appraisal as agreed with the NICE Technical Team. A summary dossier is provided, and Biogen is not submitting an economic model.

Multiple sclerosis (MS) is a chronic, inflammatory disease of the central nervous system (CNS) affecting the brain and spinal cord;[10] typically diagnosed between 20 to 40 years of age it is the leading cause of non-traumatic neurological disability in young adults.[11, 12]

- MS results in neurological impairment and physical disability that becomes irreversible over time, as the disease advances, symptoms progressively worsen affecting social and family life, activities of daily living and the ability to work[13]
- Patients with RRMS experience disease activity of clinical relapses and MRI activity, followed by periods of remission (total or partial recovery) between relapses;[10] and have frequent disease activity, resulting in a more aggressive disease course[14]

The clinical and psychological burden of MS has a substantial negative impact on the health-related quality of life (HRQoL) of patients and carers.[15–17]

- The chronic and progressive nature of MS and early age of diagnosis results in a substantial economic and societal burden[13, 16, 18]

There is increasing evidence including data from randomised controlled trials (RCTs) demonstrating early intervention with high-efficacy DMTs leads to a greater reduction in long-term disease progression.[19–23]

- DMTs are typically distinguished as either low/moderate-efficacy treatments (e.g. glatiramer acetate [GA], interferon beta [β]-1a and interferon β-1b) or high-efficacy treatments (e.g. natalizumab-TYS, ocrelizumab, ofatumumab, ponesimod, cladribine, fingolimod and alemtuzumab)
- In clinical practice for patients with highly active disease despite a full and adequate course of treatment with ≥1 DMT, current high-efficacy DMT options include ocrelizumab, ofatumumab, cladribine and ponesimod
- [redacted],[6] as such fingolimod is not considered a comparator to natalizumab-TYS
- Autologous haematopoietic stem cell transplantation (AHSCT) and alemtuzumab are considered as last-line therapies when other high-efficacy DMT options have been exhausted (UK clinical opinion)[3–5] and are not considered relevant comparators to natalizumab-TYS
- Low-moderate-efficacy DMTs (e.g. GA, interferon β-1a and interferon β-1b) are rarely used for patients with highly active RRMS due to the availability of high-efficacy DMTs (UK clinical opinion)[3–5] and are not considered relevant comparators to natalizumab-TYS

There remains a high unmet need for a range of effective and well-tolerated high-efficacy DMTs for the subpopulation of patients with highly active disease despite a full and adequate course of treatment with ≥1 DMT providing equitable access to DMTs as the more severe subpopulation of patients with highly active RRMS (i.e. RES RRMS).

- It is important that patients and healthcare professionals (HCPs) have access to various DMTs to facilitate personalised treatment decisions, personalised treatment is particularly relevant for patients with highly active RRMS, who have an aggressive disease course
- Duration of washout and risk of return of disease activity are important factors for HCPs to consider when individualising patient therapy
- There is a need for DMT options that can be used during pregnancy and breastfeeding given the young age of diagnosis
- DMTs that do not impair vaccine responses and have a favourable safety profile during vaccination schedules will help avoid delays in initiation of treatment

Natalizumab-TYS is a high-efficacy DMT (humanised monoclonal antibody).

- Natalizumab-TYS is licensed for the treatment of adults with highly active RRMS for the following patient groups:[1, 2]
    - Patients with highly active disease despite a full and adequate course of treatment with ≥1 DMT

    or

    - Patients with RES RRMS defined by two or more disabling relapses in one year, and with one or more Gd+ lesions on brain MRI or a significant increase in T2 lesion load as compared to a previous recent MRI
- The RES RRMS subpopulation is not in scope for this appraisal as natalizumab-TYS is already recommended by NICE for patients with RES RRMS
- NHS England extended the use of natalizumab-TYS to patients with highly active RRMS who initiated treatment during the COVID-19 pandemic, these patients could remain on natalizumab-TYS treatment, as such natalizumab-TYS is currently used in clinical practice for some patients with highly active RRMS with highly active disease despite a full and adequate course of treatment with ≥1 DMT
- Natalizumab-TYS is available as an intravenous (IV) and subcutaneous (SC) formulation, the SC formulation provides benefits to patients and the NHS (Section B.2.6)

To manage progressive multifocal leukoencephalopathy (PML) risk Biogen provides the StratifyJCV™ service free of charge.

- Stratify anti-JCV antibody assay test, cerebrospinal fluid [CSF] JCV deoxyribonucleic acid [DNA] test and a PML risk stratification algorithm) for HCPs who are treating or intending to treat patients with natalizumab-TYS (not for HCPs who are treating or intending to treat patients with natalizumab biosimilar [Tyruko®] referred to throughout this submission as natalizumab-TYR)

Extended interval dosing (EID) administering natalizumab-TYS IV or SC every 6 weeks (Q6W) or every 8 weeks (Q8W) instead of standard interval dosing (SID) every 4 weeks (Q4W) is used in clinical practice (UK clinical opinion)[4, 5] for some patients (e.g. to reduce the risk of PML or during pregnancy).

- EID dosing provides cost savings to the NHS (drug costs and HCP time for drug administration) and a reduction in travel and in-clinic time for patients and carers for drug administration

The UK consensus on pregnancy in MS Association of British Neurologists' (ABN) guidelines state that natalizumab-TYS can be used during pregnancy (up to 34 weeks).[24]

Natalizumab-TYS is immunogenic and has a favourable safety profile regardless of treatment length in patients with MS including patients with highly active disease.[25]

B.1.2 Description of the technology being appraised

The summary of product characteristics (SmPC) for the IV and SC formulations of natalizumab-TYS and the UK Medicines and Healthcare products Regulatory Agency (MHRA) public assessment report for the SC formulation are provided in Appendix C.

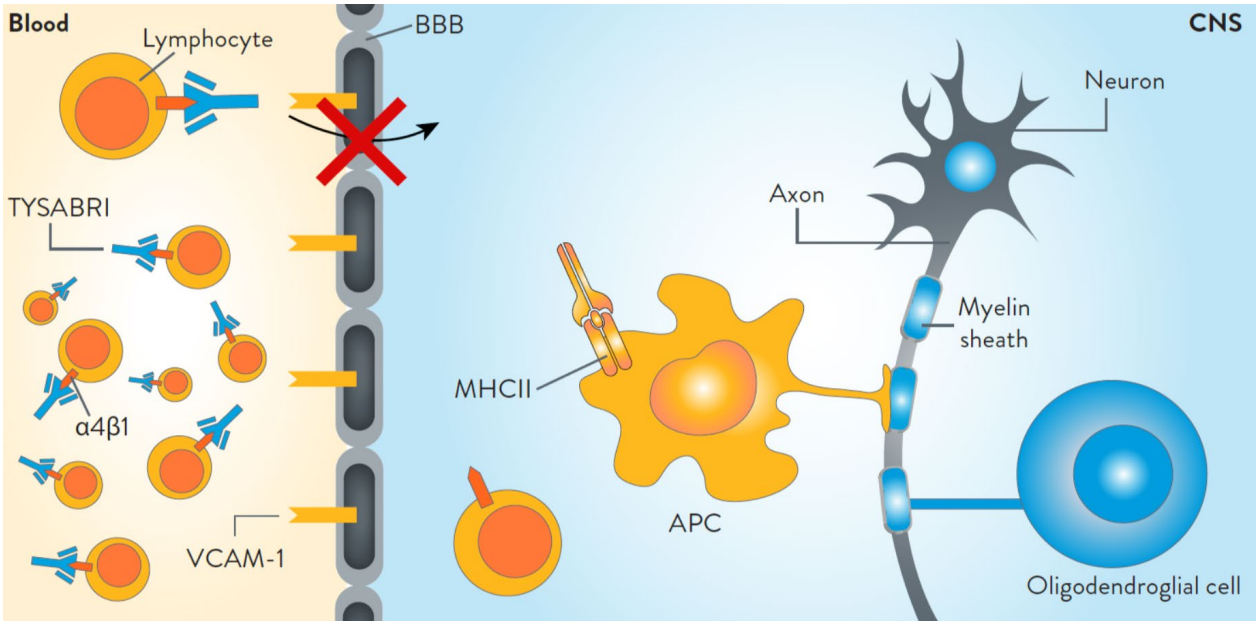
Table 2: Technology being appraised

UK approved name and brand name	Natalizumab (Tysabri®)
Mechanism of action	Natalizumab-TYS is a humanised monoclonal antibody and is the first-in-class selective adhesion-molecule inhibitor. Natalizumab-TYS binds to the α 4-ubunit of human integrins, which is highly expressed on the surface of all leukocytes, with the exception of neutrophils. Specifically, natalizumab-TYS binds the α4β1 integrin, blocking its interaction with its cognate receptor, VCAM-1, and ligands osteopontin and an alternatively spliced domain of fibronectin, CS-1 (Figure 1). Natalizumab-TYS blocks the interaction of α 4β7 integrin with the MadCAM-1. Disruption of these molecular interactions prevents transmigration of leukocytes across the endothelium into inflamed parenchymal tissue. A further mechanism of action of natalizumab-TYS may be to suppress ongoing inflammatory reactions in diseased tissues by inhibiting the interaction of α 4-expressing leukocytes with their ligands in the extracellular matrix and on parenchymal cells. As such, natalizumab-TYS may act to suppress inflammatory activity present at the disease site and inhibit further recruitment of immune cells into inflamed tissues.
Marketing authorisation/CE mark status	• Natalizumab-TYS 300 mg IV was granted EMA marketing authorisation on 27th June 2006 • Natalizumab-TYS 300 mg IV was granted MHRA marketing authorisation on 1st January 2021 • Natalizumab-TYS 2 x 150 mg SC was granted MHRA marketing authorisation on 1st April 2021
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Natalizumab-TYS is indicated as a single DMT in adults with highly active RRMS for the following patient groups: • Patients with highly active disease despite a full and adequate course of treatment with at least one DMT or • Patients with RES RRMS defined by two or more disabling relapses in one year, and with one or more Gd-enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to a previous recent MRI
Method of administration and dosage	Administration is to be performed by a healthcare professional:

	• Natalizumab-TYS 300 mg is administered by IV infusion once every 4 weeks • Natalizumab-TYS 300 mg is administered as a SC injection once every 4 weeks (as each pre-filled syringe contains 150 mg natalizumab-TYS, 2 pre-filled syringes need to be administered) Any switch in route of administration should be made 4 weeks after the previous dose. Extended interval dosing of natalizumab-TYS is included in the SmPC (Section 5.1) and is used in clinical practice to reduce the risk of PML and to reduce natalizumab-TYS exposure during pregnancy. Therefore, the average number of doses used in clinical practice should be used when calculating the medicines acquisition cost (Section B.1.2.1).
Additional tests or investigations	Anti-JCV testing: • Testing for serum anti-JCV antibody prior to initiating therapy or in patients receiving natalizumab-TYS with an unknown antibody status is recommended • Anti-JCV antibody negative patients may still be at risk of PML for reasons such as a new JCV infection, fluctuating antibody status or a false negative test result • Re-testing of anti-JCV antibody negative patients every 6 months is recommended; retesting low index patients who have no history of prior immunosuppressant use every 6 months once they reach the 2-year treatment point is recommended • Anti-JCV antibody testing is supplied by Biogen free of charge exclusively for patients on/considering natalizumab-TYS (see Section B.1.2.2 and Section B.2.6.2 for further details) MRI: • Before initiation of natalizumab-TYS a recent (usually within 3 months) MRI should be available as a reference and be repeated on a yearly basis
List price and average cost of a course of treatment	• The list price of natalizumab-TYS 300 mg concentrate for solution for infusion is £1,130 per vial • The list price of natalizumab-TYS 150 mg solution for injection in a pre-filled syringe is £1,130 (for 2 x 150 mg syringes) • Total cost per patient/year based on standard interval dosing of natalizumab-TYS IV or SC (every 4 weeks): £14,690.00 (13 doses) • Total cost per patient/year based on extended interval dosing of natalizumab-TYS IV or SC : [redacted][26]
Patient access scheme (if applicable)	No patient access scheme is approved for natalizumab-TYS. [redacted]

Abbreviations: BNF, British National Formulary; CS-1, connecting segment-1; DMT, disease-modifying therapy; EMA, European Medicines Agency; Gd, gadolinium; IV, intravenous; JCV, John Cunningham virus; MadCAM-1, mucosal addressin cell adhesion molecule-1; MHRA, Medicines and Healthcare products Regulatory Agency; MRI, magnetic resonance imaging; MS, multiple sclerosis; Natalizumab-TYS, natalizumab (Tysabri®); PML, progressive multifocal leukoencephalopathy; RES RRMS, rapidly evolving severe relapsing–remitting multiple sclerosis; SC, subcutaneous; SmPC, summary of product characteristics; VCAM-1, vascular cell adhesion molecule-1
Source: Natalizumab-TYS SmPC[1, 2]; BNF online[27]

Figure 1: Natalizumab-TYS mechanism of action



Abbreviations: APC, antigen-presenting cell; BBB, blood brain barrier; CNS, central nervous system, MHCII, major histocompatibility complex class II; natalizumab-TYS, natalizumab (Tysabri®); VCAM-1, vascular cell adhesion molecule-1
Source: BiogenLinc™ website[28]

B.1.2.1 Extended interval dosing

EID, administering natalizumab-TYS IV or SC Q6W or Q8W instead of SID Q4W is used in clinical practice for some patients (UK clinical opinion).[4, 5] Although EID is not included in the natalizumab-TYS licensed indication, EID (Q6W) is outlined in the natalizumab-TYS SmPC.[1, 2]

EID provides the following benefits:

1. Cost savings to the NHS (drug costs and HCP time for drug administration).
2. A reduction in natalizumab-TYS exposure during pregnancy.
3. A reduction in the risk of PML (Section B.2.5.3.1).
4. A reduction in travel and in-clinic time for some patients and carers for drug administration.

From an economic perspective natalizumab-TYS EID decreases the number of IV infusions or SC injections required per patient/year, reducing the cost of natalizumab-TYS to the NHS. In clinical practice [redacted][26] doses of natalizumab-TYS are administered per patient/year [redacted] with EID, compared to SID (13 doses per patient/year, [redacted]. Additional NHS savings are also achieved due to the reduction in HCP time needed for drug administration.

The UK consensus on pregnancy in MS ABN guidelines, state the frequency of natalizumab-TYS doses can be lowered to Q8W to reduce natalizumab-TYS exposure throughout pregnancy (see Section B.1.2.3 for further information on DMT use during pregnancy).[24]

A number of DMTs are associated with an increased risk of developing PML including fingolimod, ocrelizumab, alemtuzumab and natalizumab-TYS.[29] Specific risk management for PML in patients treated with natalizumab-TYS includes regularly monitoring throughout treatment and instructions for patients and caregivers on the early signs and symptoms of PML. A longer time between natalizumab-TYS doses may reduce the blood levels of natalizumab-TYS to sufficiently allow some immune cells to pass into the brain and prevent PML. Findings from a Phase 3b RCT (NOVA) suggest that most patients who receive a stable dose of natalizumab-TYS (Q4W) can switch to natalizumab-TYS (Q6W) without any meaningful loss of efficacy and safety (see Section B.2.5.3.1).[30]

B.1.2.2 StratifyJCV™ service

To manage PML risk Biogen provides the StratifyJCV™ service free of charge (Stratify anti-JCV antibody assay test, CSF JCV DNA test and a PML risk stratification algorithm). StratifyJCV™ is for HCPs who are treating or intending to treat patients with natalizumab-TYS and not for HCPs who are treating or intending to treat patients with the natalizumab biosimilar (natalizumab-TYR).

The StratifyJCV™ PML risk stratification algorithm is based on a pooled patient cohort comprised of approximately 37,000 natalizumab-TYS treated patients who participated in natalizumab-TYS studies. The evidence for the risk stratification algorithm is specific to the StratifyJCV™ tests. Further details on the StratifyJCV™ service are provided in Section B.2.6.2.

B.1.2.3 Pregnancy

The risk-benefit profiles of DMTs during pregnancy vary, and for most DMTs it is generally recommended that women stop treatment before conception and restart after breastfeeding.

The ABN guidelines do not recommend the use of fingolimod, cladribine, and alemtuzumab during pregnancy.[24] Although ponesimod is not mentioned in the guidelines, it is contraindicated during pregnancy.[9]

Only three high-efficacy DMTs are recommended for use by ABN guidelines during pregnancy (natalizumab-TYS, ocrelizumab and ofatumumab).[24, 31] Natalizumab-TYS can be used during pregnancy (up to 34 weeks).[24] The SmPC for natalizumab-TYS states that a risk-benefit evaluation on the use of natalizumab-TYS during pregnancy should take into account the patient's clinical condition and the possible return of disease activity after stopping treatment.[1, 2]

B.1.2.4 Immunogenicity and safety

High-efficacy DMTs may increase the risk of infections and, where necessary, vaccinations should be administered to mitigate this risk.[25] Some vaccinations require multiple doses administered at intervals (e.g. hepatitis B vaccination includes 3 or 4 doses with 6-month intervals).[25] The immunogenicity and safety of vaccinations in patients with highly active

RRMS (e.g. hepatitis B, hepatitis C and COVID-19) can be compromised by some DMTs, specifically anti-CD20 therapies (e.g. ocrelizumab and ofatumumab).[25] Therefore, in clinical practice these DMTs are usually delayed until vaccination schedules are complete. Additionally, reports of disease worsening following vaccinations highlight concerns about vaccination safety.[25] Considering patients with highly active RRMS have a more aggressive disease it is important to avoid treatment delays due to vaccination.

Natalizumab-TYS generates a unique immune response, reversibility of natalizumab-TYS effects on peripheral immune cells return to normal levels within 16 to 20 weeks after the last dose.[32] Conversely cell depleting agents are not readily reversible and have a long-lasting impact on the immune system. As a result, natalizumab-TYS appears to preserve immune responses to both naïve and recall antigens. The natalizumab-TYS SmPC states: "In a randomised, open label study of 60 patients with relapsing MS there was no significant difference in the humoral immune response to a recall antigen (tetanus toxoid) and only slightly slower and reduced humoral immune response to a neoantigen (keyhole limpet haemocyanin) was observed in patients who were treated with this medicinal product for 6 months compared to an untreated control group."[1, 2]

Immunisation with inactivated vaccines (including hepatitis B, hepatitis C and COVID-19) with natalizumab-TYS treatment is immunogenic and has a favourable safety profile regardless of treatment length in patients with MS including patients with highly active disease.[25] As such, natalizumab-TYS provides a valuable treatment option for patients with highly active RRMS who require vaccines, avoiding delays in DMT initiation.[25]

Furthermore, as immunisation with inactivated COVID-19 vaccines with natalizumab-TYS treatment is immunogenic and has a favourable safety profile, NHS England expanded its use for patients with highly active RRMS during the COVID-19 pandemic.

B.1.2.5 Secure, safe and environmentally sustainable supply chain

Biogen put an emphasis on excellent manufacturing processes and uninterrupted track of supply record and have a secure and safe supply chain that is controlled end-to-end. We follow strict regulations to ensure patient safety as it is our number one priority, and we take the issue of counterfeit and falsified drugs very seriously. To ensure a resilient, long-term supply flow, Biogen has various processes in place, such as regular risk assessments and maintenance of healthy inventories across our end-to-end process. Biogen runs and operates two world class manufacturing plants in the US and in Europe as well as managing the supply chain globally (in regard to regulation, quality, clinical trials, product quality monitoring in the supply chain etc.). The extensive manufacturing capacity and network of qualified suppliers allows Biogen to manage and implement risk-based redundancies for critical elements within the supply chain. To this day, there has not been any supply shortage of natalizumab-TYS as Biogen strives for an excellent and reliable delivery service.

The Contract Manufacturing Organisation (CMO) responsible for the manufacturing and packaging of natalizumab-TYS IV is committing to reduce the CO2 emissions by 50% in 2030 and be carbon-neutral by 2040. Our CMOs involved in the manufacturing and packaging of natalizumab-TYS SC have equally ambitious emissions reduction policies and targets - since 2021, all Vetter sites worldwide have been CO2-neutral. By realising

efficiency measures, Vetter has saved more than 31 million KWh of energy over the past ten years and expects to further reduce energy consumption by an additional 10% by 2029.

B.1.3 Health condition and position of the technology in the treatment pathway

B.1.3.1 Disease overview

MS is a chronic, inflammatory disease of the CNS affecting the brain and spinal cord.[10] The disease is typically diagnosed between 20 to 40 years of age and is the leading cause of non-traumatic neurological disability in young adults.[11, 12] It is estimated that over 150,000 people (1 in every 400 people) in the UK have MS and approximately 7,100 people are newly diagnosed each year (2022 data).[33] Prevalence of MS is higher in women than men and 71% of people diagnosed with MS in the UK are women.[33]

MS results in neurological impairment and physical disability that becomes irreversible over time. The disease course of MS is highly variable, and the timing of relapses or disability progression are unpredictable. As the disease advances, symptoms progressively worsen including fatigue, impaired mobility, visual disturbances, disability and cognitive decline; which affects social and family life, activities of daily living and the ability to work.[13] Furthermore, MS negatively impacts emotional wellbeing and high levels of depression are seen at key stages of disease progression.[13] Approximately 50% of patients with MS experience major depression at some point in their life, increasing the risk of suicidal ideation and death by suicide.[13, 34] As the disease progress individuals with MS will become more dependent on carers who take on responsibilities that can be physically and emotionally demanding impacting caregivers' daily life and emotional wellbeing.[35, 36]

The clinical and psychological burden of MS has a substantial negative impact on the HRQoL of patients and carers. Patients with MS report a rapid decline in health status early in the disease course, which continues to worsen with increasing disability. Mean (standard deviation [SD]) EuroQoL-5 Dimension-3 Level (EQ-5D-3L) scores for patients with MS taken from two large UK studies are presented in Table 3.

Table 3: EQ-5D-3L scores of patients with MS (UK population)

HRQoL measurement	Heather et al. (2023)[15] N=14,385	Thompson et al. (2017)[16] N=799
Mean EQ-5D-3L score (SD)	0.562 (0.308)	0.469 (0.3)
EDSS score 0	0.906	0.898
EDSS score 8 or 8.5	0.160	0.157*

Abbreviations: EDSS, Expanded Disability Status Scale; EQ-5D-3L, Euroqol-5 Dimension-3 Level; SD, standard deviation

* EDSS score 8 only

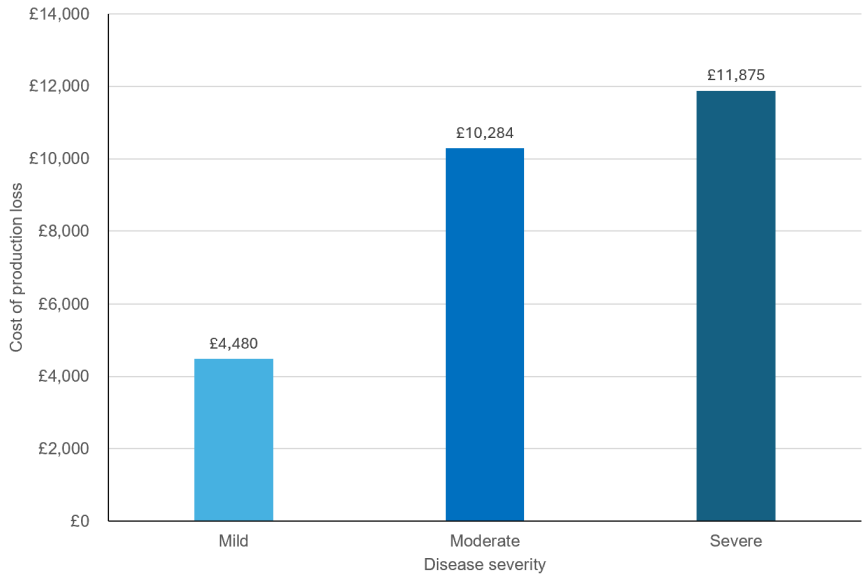
Source: Heather et al. (2023)[15]; Thompson et al. (2017)[16]

In a UK cross-sectional observational study (n=200 caregivers of people with MS and 200 matched controls), caregivers reported significantly lower HRQoL, as measured by EQ-5D,

compared to matched controls (p=0.003),[17] highlighting the importance of considering the HRQoL of caregivers in economic evaluations.

The chronic and progressive nature of MS and early age of diagnosis results in a substantial economic and societal burden. In the UK, the cost of MS is estimated at £1.4 billion per year.[18] A literature review on societal costs of MS suggests that 55% of MS costs are indirect, highlighting the cost of lost working capacity.[13] In a UK cross-sectional retrospective study of patients with MS (n=779); total mean costs of production loss increased with MS disease severity (Figure 2). Mean costs of production loss equated to 38%, 45%, and 33% of total mean costs for mild, moderate and severe disease, respectively.[16]

Figure 2: Mean costs of production loss per patient/year



Source: Thompson et al. (2017)[16]

Despite the heterogenous nature of MS, the clinical course of MS falls into four main subtypes; clinically isolated syndrome (CIS), RRMS, secondary progressive multiple sclerosis (SPMS) and primary progressive multiple sclerosis (PPMS).[10] Approximately 85% of patients with MS will initially present with RRMS and around 50% of these patients will transition to SPMS within 20 years without treatment.[10] Patients with RRMS experience disease activity of clinical relapses (new or worsening of symptoms) and MRI activity (Gd+ lesions or new or enlarging T2 lesions), followed by periods of remission (total or partial recovery) between relapses.[10]

Patients with highly active RRMS have more frequent disease activity (clinical relapses and MRI activity), resulting in a more aggressive disease course, i.e. rapid progression of physical disability and neurological impairment, despite treatment.[14] **For this submission the highly active RRMS patient population is defined as patients with highly active disease despite a full and adequate course of treatment with ≥1 DMT.** While this population also includes those patients with highly active RRMS (RES RRMS), natalizumab-

TYS is already recommended as a treatment option by NICE for patients with RES RRMS (TA127).

B.1.3.2 Current treatment pathway for patients with highly active RRMS with highly active disease despite a full and adequate course of treatment with ≥1 DMT

There is no cure for MS[19], the primary goals of treatment with DMTs are to reduce disease activity, delay disability progression and improve HRQoL.

As the clinical course of RRMS is highly variable for each patient, a range of DMTs options are needed to personalise treatment based on the individual needs of the patient. Choosing the most appropriate DMT requires consideration of numerous factors including: the risk–benefit profiles of DMTs, patient demographics (e.g. age, gender), clinical factors (e.g. activity pattern, disability accrued, existing comorbidities), patient preference (e.g. route of administration, dosing frequency) and lifestyle. Duration of washout and risk of return of disease activity are important factors for HCPs to consider when individualising patient therapy. Natalizumab-TYS has a shorter washout period allowing more flexibility compared to CD20 therapies.[37, 38]

DMTs are typically distinguished as either low/moderate-efficacy treatments (e.g. GA, interferon beta β-1a and interferon β-1b) or high-efficacy treatments (e.g. natalizumab-TYS, ocrelizumab, ofatumumab, ponesimod, cladribine, fingolimod and alemtuzumab). Currently available high-efficacy DMTs differ with regard to licensed indications, formulations, and NICE recommendations (Table 4).

In MS there is a narrow 'window of opportunity' to treat in the early stages of disease before irreversible neurological damage occurs.[39] There is increasing evidence including data from RCTs demonstrating early intervention with high-efficacy DMTs leads to a greater reduction in long-term disease progression.[19–23] A 'hit hard and early' strategy with high-efficacy DMTs is increasingly preferred and is particularly important for patients with highly active disease.[39]

The updated ABN guidance for the use of DMTs in MS (2024) recommends that:[40]

- Patients with active disease should be offered and have access to all DMTs for which they are eligible as soon as possible
- High-efficacy therapy should be considered as first option in eligible patients

The NHS England treatment algorithm for MS DMTs (2023) provides a treatment pathway for patients with disease activity despite initial treatment with a DMT (low/moderate-efficacy and high-efficacy DMTs). After failure of a DMT, treatment options include high-efficacy DMTs: ocrelizumab, ofatumumab, ponesimod, cladribine, fingolimod, alemtuzumab and AHSCT.[41] However, this algorithm adheres to NICE recommendations for DMTs, many of which were published over decade ago and may not represent the perceptions of best clinical practice today.[40]

B.1.3.2.1 Current treatment pathway for patients with highly active RRMS with highly active disease despite a full and adequate course of treatment with ≥1 DMT

The current treatment pathway in clinical practice for patients with highly active RRMS who have active disease despite a full and adequate course of treatment with ≥1 DMT is outlined in Figure 3. For this patient population, high-efficacy DMT options include ocrelizumab, ofatumumab, cladribine and ponesimod. If a patient becomes intolerant to or continues to experience relapse with a particular DMT they will switch to an alternative DMT (typically after 6 months).

Although fingolimod, alemtuzumab and AHSCT are listed as comparators in the final scope for this appraisal, they are not considered relevant comparators to natalizumab-TYS for the highly active RRMS population.

[redacted],[6] as such fingolimod is not considered a comparator to natalizumab-TYS. Fingolimod use is expected to decline further in the future due to the requirement for CV and skin lesion monitoring (UK clinical opinion).[3–5]

AHSCT and alemtuzumab are considered as last-line therapies when other DMT options have been exhausted (UK clinical opinion).[3–5] AHSCT is only available in a small number of NHS centres and very few people with MS are accepted for treatment.[7, 8] Alemtuzumab is associated with possible serious adverse events (SAEs), including thyroid disorders, immune thrombocytopenic purpura (ITP) and kidney disease.[9]

Low/moderate efficacy DMTs (e.g. GA, interferon β-1a and interferon β-1b) were comparators in the natalizumab-TYS submission for patients with RES RRMS (TA127). At the time of this appraisal (2007) treatment options were limited for patients with highly active disease. However, they are now rarely used in clinical practice due to the current availability of high-efficacy DMTs (UK clinical opinion)[3–5] and are not considered relevant comparators to natalizumab-TYS.

Table 4: High-efficacy DMTs licensed indications and NICE recommendations specific to this submission

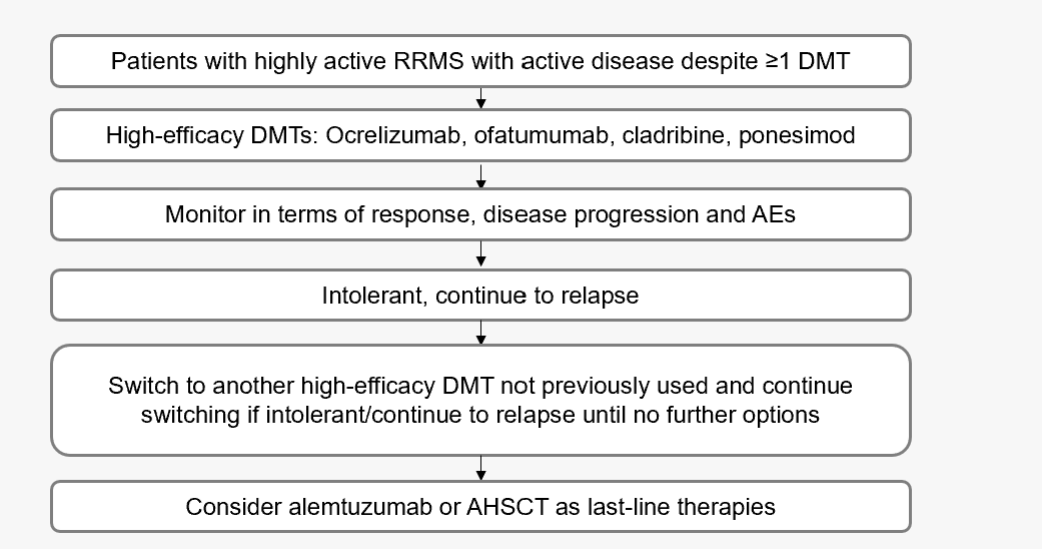
Drug	Formulation	Licensed indication (specific to the patient population for this submission)*	NICE ID (date)	NICE recommendation (specific to the patient population for this submission)
Ocrelizumab	IV infusion	Adult patients with RMS with active disease defined by clinical or imaging	TA563 (25th July 2018)	Ocrelizumab is recommended as an option for treating RRMS in adults with active disease defined by clinical or imaging features, only if alemtuzumab is contraindicated or otherwise unsuitable and the company provides ocrelizumab according to the commercial arrangement.
Ofatumumab	Pre-filled pen		TA699 (19th May 2021)	Ofatumumab is recommended as an option for treating RRMS in adults with active disease defined by clinical or imaging features. This is only if the company provides ofatumumab according to the commercial arrangement.
Ponesimod	Film-coated tablet		TA767 (2nd February 2022)	Ponesimod is recommended as an option for treating RRMS in adults with active disease defined by clinical or imaging features. This is only if the company provides ponesimod according to the commercial arrangement.
Cladribine	Tablet		TA616 (19th December 2019; updated 21st May 2024)	Cladribine is recommended as an option for treating highly active MS in adults, only if the person has RRMS that has responded inadequately to treatment with DMT, defined as 1 relapse in the previous year and MRI evidence of disease activity.
Alemtuzumab	IV infusion	Adults with highly active RRMS: Patients with highly active disease despite a full and adequate course of treatment with ≥1 DMT	TA312 (28th May 2014; updated 21st May 2024)	Alemtuzumab is recommended as an option, within its marketing authorisation, for treating highly active relapsing–remitting multiple sclerosis in adults with highly active disease despite a full and adequate course of treatment with ≥1 DMT.
Fingolimod	Capsule	Adults and paediatric patients (10 years and older) with highly active RRMS: Patients with highly active disease despite a full and adequate course of treatment with ≥1 DMT	TA254 (25th April 2012)	Fingolimod is recommended as an option for the treatment of highly active RRMS in adults, only if they have an unchanged or increased relapse rate or ongoing severe relapses compared with the previous year despite treatment with beta interferon, and the manufacturer provides fingolimod with the discount agreed as part of the patient access scheme.

Abbreviations: DMT, disease-modifying therapy; ID, identification; IV, intravenous; NICE, National Institute of Health and Care Excellence; RMS, relapsing multiple sclerosis; RRMS, relapsing–remitting multiple sclerosis; TA, technology appraisal

* Licensed indications and NICE recommendations are presented only for the population of interest for this submission, some DMTs have broader licensed indications and NICE recommendations.

Source: NICE website and SmPCs

Figure 3: UK treatment pathway for highly active RRMS with highly active disease despite a full and adequate course of treatment with ≥1 DMT*



Abbreviations: AEs, adverse events; AHSCT, autologous haematopoietic stem cell transplantation; DMT, disease-modifying therapy; RES, rapidly evolving severe; RRMS, relapsing–remitting multiple sclerosis
* The patient pathway excludes patients with highly active RES RRMS.

B.1.3.3 Unmet need

There remains a high unmet need for a range of effective and well-tolerated high-efficacy DMTs for the population of patients with highly active RRMS (i.e. with highly active disease despite a full and adequate course of treatment with ≥1 DMT) thereby providing equitable access to therapies as the more severe subpopulation of patients with rapidly evolving severe RRMS (i.e. RES RRMS).

Zero tolerance to disease activity in MS is important and escalating early in the treatment course to a DMT with strong and sustained efficacy helps preserve function and delay disease progression.

Currently available high-efficacy DMTs differ with regard to their licensed indications, methods of administration, monitoring requirements, AE profiles and NICE recommendations. It is important that patients and HCPs have access to various DMTs to facilitate personalised treatment decisions for patients with highly active RRMS. Personalised treatment is particularly relevant for patients with highly active RRMS, who have an aggressive disease course and is also identified as a priority in the NHS Long Term Plan.[42] Duration of washout and risk of return of disease activity are important factors for HCPs to consider when individualising patient therapy.

Furthermore, given the young age at diagnosis, many women with highly active RRMS may wish to continue or start a family. As such, there is a need for DMT options that can potentially be used during pregnancy and breastfeeding.

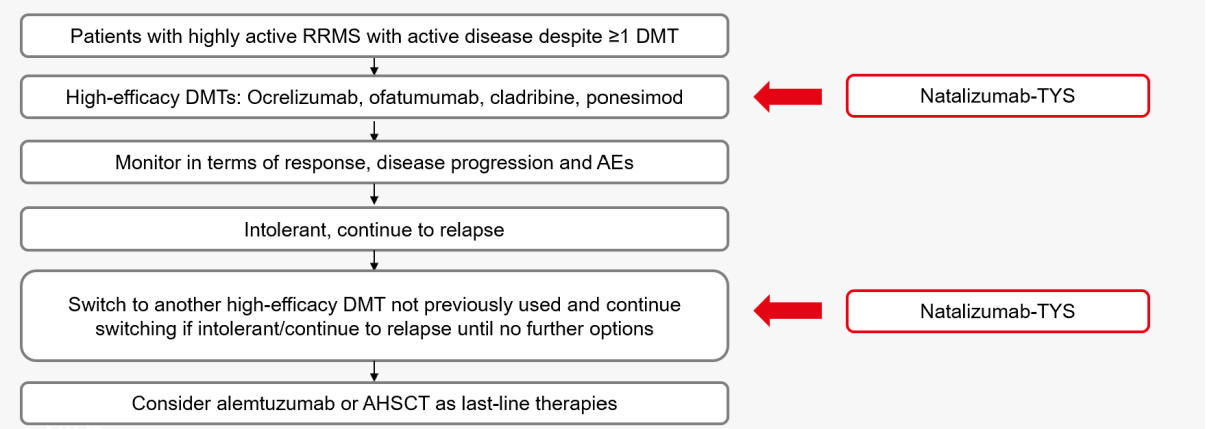
The immunogenicity and safety of vaccinations in patients with highly active RRMS (e.g. hepatitis B, hepatitis C and COVID-19) can be compromised by some DMTs, specifically anti-CD20 therapies (e.g. ocrelizumab and ofatumumab).[25] Therefore, in clinical practice these DMTs are usually delayed until vaccination schedules are complete. As early

intervention with high-efficacy DMTs is important for patients with highly active RRMS there is a need for DMTs that do not impair vaccine responses and have a favourable safety profile during vaccination schedules.

B.1.3.4 Proposed place of natalizumab-TYS in the treatment pathway

The proposed place of natalizumab-TYS is for the treatment of highly active RRMS in patients with highly active disease despite a full and adequate course of treatment with ≥1 DMT. Natalizumab-TYS is already recommended as a treatment option by the NICE for patients with RES RRMS (TA127). In clinical practice natalizumab-TYS can be used as an alternative treatment to ocrelizumab, ofatumumab, cladribine and ponesimod and prior to last line therapies, alemtuzumab and AHSCT (Figure 4).

Figure 4: Proposed place of natalizumab-TYS in the UK treatment pathway for highly active RRMS with highly active disease despite a full and adequate course of treatment with ≥1 DMT



Abbreviations: AEs, adverse events; AHSCT, autologous haematopoietic stem cell transplantation; DMT, disease-modifying therapy; natalizumab-TYS, natalizumab (Tysabri®); RRMS, relapsing–remitting multiple sclerosis

B.1.4 Equality considerations

No equality issues are anticipated for the appraisal of natalizumab-TYS for patients with highly active RRMS with highly active disease despite a full and adequate course of treatment with ≥1 DMT.

B.2 Clinical effectiveness

SUMMARY

The efficacy and safety of natalizumab-TYS has been studied across randomised controlled RCTs and real-world settings for >15 years; globally 269,687 patients (as of 31 December 2023) have been treated with natalizumab-TYS IV and SC.[43]

- There are no RCTs that compare natalizumab-TYS monotherapy with other DMTs for patients with highly active RRMS who have highly active disease despite a full and adequate course of treatment with ≥1 DMT

The primary clinical and safety evidence in this submission is provided by (1) non-RCT studies in patients with highly active RRMS, identified by a targeted literature review in 2023,[44] **(2) the Tysabri® Observational Program (TOP) the largest real-world study of natalizumab-TYS**[45, 46] **and (3) supportive studies.**[30, 47–50]

Results from the meta-analyses of the non-RCTs included in the literature review demonstrate lower relapse rates, disease activity and radiological (MRI) outcomes with natalizumab-TYS vs. platform DMTs and the high-efficacy DMT, fingolimod in patients with highly active RRMS despite a full and adequate course of treatment with ≥1 DMT and ≥1 relapse in the prior year.[44]

- Although fingolimod is not considered a comparator to natalizumab-TYS, due to its limited use in routine clinical practice, the meta-analysis demonstrates the effectiveness and safety of natalizumab-TYS vs. a high-efficacy DMT for the treatment of patients with highly active RRMS

Results from the TOP 15-year analysis demonstrated long-term control of RRMS disease activity in patients receiving natalizumab-TYS regardless of prior number of DMTs.[45, 46]

- In the TOP study, 72.4% and 92.6% of patients in the UK (n=134) and global (n=6,321) populations had ≥1 prior DMT, baseline data suggests the UK population had a more aggressive disease course than patients in the global population[45, 46]
- In the UK and global populations at 15 years significant annualised relapse rate (ARR) reductions were observed with natalizumab-TYS treatment (93.2% and 91.0%, respectively [p<0.0001 for both] compared to the year prior to natalizumab initiation)[46]
- At 10.5 years the cumulative probability of CDW and CDI was 60.3% and 46.3%, in the UK population, respectively and 40.7% and 35.2% in the global population, respectively (UK sample size was low at 10.5 years)[46]
- In the global population at 15 years, the cumulative probability of CDW and CDI were 42.9% and 39.6%, respectively (the number of patients at risk after 13 years was low).[45] At 13 years, the cumulative probabilities of CDW and CDI were 42.9% and 35.9%, respectively
- There were no new safety signals identified over 15 years; the incidence of opportunistic infections, PML, and malignancies was low[45]

In a *post-hoc* subgroup analysis of the TOP study of patients who had received prior treatment with ≥1 DMT and had experienced 1 relapse (n=[redacted]) the mean ARR decreased from [redacted] pre-natalizumab-TYS to [redacted] post-natalizumab-TYS treatment

demonstrating that regardless of relapse in the prior year and prior DMT use natalizumab-TYS reduced the risk of relapse.[51]

The DELIVER and REFINE studies demonstrate the efficacy and safety of natalizumab-TYS SC:[49, 50]

- An analysis from the TOP study demonstrates that the efficacy and safety of natalizumab-TYS is maintained when patients switch from natalizumab-TYS IV to natalizumab-TYS SC[52]
- [redacted][53]

The NOVA study (Part 1) and a recently published systematic literature (SLR) and meta-analysis suggest that there are no significant differences in efficacy and safety of natalizumab-TYS IV EID vs. SID:[30, 54]

- The NOVA extension study (Part 2) demonstrates that the efficacy and safety of natalizumab-TYS is maintained when switching from natalizumab-TYS IV EID to natalizumab-TYS SC EID[55]

The availability of natalizumab-TYS SC provides benefits over natalizumab-TYR (Tyruko®) which is only available as an IV infusion:

- Benefits to the NHS include reduced costs for HCP time, chair time, equipment costs and increased infusion suite capacity, allowing more patients to be treated, facilitating a reduction in waiting lists
- Benefits to patients include enhanced patient choice, convenience (reduced drug administration, observation and travel time), and reduced personal expenditure (travel costs)

A number of clinical (Phase 3b NOVA extension study) and prospective real-world studies have reported high levels of patient preference for natalizumab-TYS SC.[55–58]

The efficacy and safety of natalizumab-TYS has been studied across RCTs and real-world settings for >15 years; globally 269,687 patients (as of 31 December 2023) have been treated with natalizumab-TYS IV and SC.[43]

B.2.1 Identification and selection of relevant trials

There are no RCTs that compare natalizumab-TYS monotherapy with other DMTs for patients with highly active RRMS who have highly active disease despite a full and adequate course of treatment with ≥1 DMT.

To address the evidence gap, a targeted literature review was conducted in 2023 to identify non-RCT studies assessing the efficacy and safety of natalizumab-TYS vs. 'platform DMTs' (e.g. interferon β, dimethyl fumarate, GA, or teriflunomide) and high-efficacy DMTs (e.g. alemtuzumab, ocrelizumab, cladribine or fingolimod) for the treatment of highly active RRMS.[44]

The patient population included in the literature review was adult patients (≥18 years) with RRMS who had:

- Unchanged or increased relapse rate compared with the previous year

- Failed to respond to a full and adequate course of DMT
- At least one relapse in the previous year while on therapy

This patient population (referred to as the suboptimal therapy [SOT] population in the Chappell et al. draft manuscript) is closely aligned with the patient population of interest for this submission. The non-RCT data identified demonstrates the efficacy and safety of natalizumab-TYS for the treatment of patients with highly active RRMS.

Further details on the methodology of the literature review are provided in Appendix D.

The 27 included studies (Appendix D) assessed natalizumab-TYS vs. platform DMTs and vs. the high-efficacy DMT, fingolimod for the treatment of highly active RRMS. No non-RCTs were identified for comparisons of natalizumab-TYS with ocrelizumab, alemtuzumab and cladribine.[44] These DMTs received marketing authorisation later than natalizumab-TYS and fingolimod, hence these treatments have limited published real-world data in terms of sample size and follow-up for inclusion.

B.2.2 List of relevant clinical effectiveness evidence

The primary clinical and safety evidence supporting the use of natalizumab-TYS for the treatment of patients with highly active RRMS with highly active disease despite a full and adequate course of treatment with ≥1 DMT in this submission is provided by (1) the non-RCT studies in patients with highly active RRMS included in the literature review, (2) the TOP study 15-year final analysis and (3) supportive studies (Table 5).

The literature review included the 10-year interim analysis of the largest real-world study of natalizumab-TYS evaluating the long-term safety and efficacy of natalizumab-TYS in patients with RRMS (n=6,148) with follow-up to 15 years.[59] The 5-year interim analysis of the TOP study was the pivotal efficacy and safety evidence presented to the European Medicines Agency (EMA) for the extension of the licensed indication of natalizumab-TYS from patients with “high disease activity despite treatment with a beta interferon or GA” to with “highly active disease despite a full and active course of treatment with ≥1 DMT”.[60] The 15-year final analysis extends the 5-year data with a larger cohort of patients and a longer duration of natalizumab-TYS treatment (Section B.2.5.1). In the UK and global populations, most patients (72.4% and 92.6%) in the 15-year analysis had received ≥1 prior DMT, respectively.[45, 46]

The non-RCT efficacy and safety data for natalizumab-TYS in patients with highly active RRMS included in the literature review are presented in the supplementary data tables (S1 to S13) in the Chappell et al. draft manuscript.[44]

Meta-analyses of the non-RCTs included in the literature review were performed to compare the efficacy and safety of natalizumab-TYS with platform DMTs and fingolimod in patients with highly active RRMS.[44] Results from the meta-analyses demonstrate lower relapse rates, disease activity and radiological (MRI) outcomes with natalizumab-TYS vs. platform DMTs and the high-efficacy DMT, fingolimod in patients with highly active RRMS (Section B.2.7.1).[44]

Although fingolimod is not considered a comparator to natalizumab-TYS (as it is rarely used in clinical practice for patients with highly active RRMS), the meta-analysis demonstrates the effectiveness and safety of natalizumab-TYS vs. a high-efficacy DMT for the treatment of patients with highly active RRMS.

Table 5: Studies included in the submission

Study name	Relevance to the submission
Pivotal evidence	
Non-RCT studies (n=27) and meta-analyses of comparative studies (n=16) and case series (n=11)[44]	The 27 identified non-RCTs assess the efficacy and safety of natalizumab-TYS in patients with RRMS who had (1) unchanged or increased relapse rate compared with the previous year (2) failed to respond to a full and adequate course of DMT and (3) at ≥1 relapse in the previous year while on therapy (representative of patients with highly active RRMS). Results of the meta-analyses of comparative studies (n=16) demonstrate the efficacy and safety of natalizumab-TYS in the highly active RRMS population (lower relapse rates, disease activity and radiological outcomes with natalizumab-TYS vs. platform DMTs and the high-efficacy DMT, fingolimod).
TOP study (15-year final analysis, July 2007 to 1st November 2022)[45, 46]	Largest real-world study of natalizumab-TYS 300 mg IV in patients with RRMS (including patients who have had ≥1 prior DMT). The 5-year interim analysis of the TOP study was the pivotal efficacy and safety evidence presented to the European Medicines Agency for the extension of the licensed indication of natalizumab-TYS from patients with "high disease activity despite treatment with a beta interferon or GA" to "highly active disease despite a full and adequate course of treatment with ≥1 DMT".[60] The final 15-year analysis of the TOP study is provided for both the global and UK populations (the UK population was representative of patients with a more aggressive disease course than the global population) reinforcing the effectiveness and safety of natalizumab-TYS over 15 years.
Supportive evidence	
AFFIRM study[47, 48]	Demonstrates the efficacy and safety of natalizumab-TYS 300 mg IV for treating patients with RRMS (including patients with highly active RRMS, representative of the RES population)
DELIVER study[49]	Demonstrates that the PD and PK parameters and safety profile of natalizumab-TYS 300 mg SC are comparable to those of natalizumab-TYS 300 mg IV
REFINE study[50]	Demonstrates that the PD and PK parameters and efficacy and safety profiles of natalizumab-TYS 300 mg SC are comparable to those of natalizumab-TYS 300 mg SC has comparable efficacy (ARR and MRI lesions) to natalizumab-TYS 300 mg IV

NOVA study[30]	Demonstrates that patients who are stable on natalizumab-TYS 300 mg IV Q4W can switch to natalizumab-TYS 300 mg IV Q6W without any clinically meaningful loss of efficacy with comparable safety outcomes

Abbreviations: ARR, annual relapse rate; DMT, disease-modifying treatment; IV, intravenous; MRI, magnetic resonance imaging; Natalizumab-TYS, natalizumab (Tysabri®); PD, pharmacodynamics; PK, pharmacokinetics; Q4W, every 4 weeks; Q6W, every 6 weeks; RES, rapidly evolving severe; RRMS; relapsing–remitting multiple sclerosis; SC, subcutaneous

Source: Foley et al. (2022)[30]; Chappell et al. (draft manuscript)[44]; Trojano et al. (2023)[45]; Nicholas et al. (2023)[46]; Plavina et al. (2016)[49]; Trojano et al. (2021)[50]; Polman et al. (2006)[47]; Hutchinson et al. (2009)[48]

B.2.3 Summary of methodology of the relevant clinical effectiveness evidence

The methodology of the TOP study and the natalizumab-TYS supportive studies included in the submission is provided in Table 6.

Table 6: Overview and methodology of natalizumab-TYS studies included in the submission

[1]Study name	Design (status)	Location	Population (n=)	Intervention/comparators	Key inclusion criteria	Outcomes or objectives
Pivotal evidence						
TOP study (15-year final analysis)[45, 46]	15-years, multinational, multicentre, open-label, prospective observational (complete)	Argentina, Australia, Belgium, Canada, Czech Republic, Finland, France, Germany, Great Britain, Greece, Italy, Mexico, Netherlands, Norway, Portugal Slovakia, Spain	RRMS (n=6,321 global population; n=134 UK population)	Natalizumab-TYS 300 mg IV	• Diagnosis of RRMS • Natalizumab-TYS naïve or ≤3 doses of natalizumab-TYS	Primary outcome: • Long-term safety (incidence and type of SAEs) Secondary outcomes: • Disease activity measured by annualised relapse rate • Probability of 24-week confirmed disability worsening and disability improvement measured by EDSS*
Supportive evidence						
AFFIRM study[47, 48]	Phase 3, 2-year, multinational, multicentre, randomised, double-blind, placebo-controlled (complete)	Europe (including the UK), North America, Australia and New Zealand	RRMS (n=942)	• Natalizumab-TYS 300 mg IV (n=627; n=148 with high disease activity) • Placebo (n=315; n=61 with high disease activity)	• Male/female age 18 to 50 with diagnosis of RRMS • EDSS score 0.0 to 5.0 • 1 relapse within prior year to randomisation • MRI scan demonstrating lesions consistent with MS	Primary outcome: • ARR at year 1 • Disability progression at year 2 Secondary outcomes: • ARR at year 2 • Proportion of relapse free patients at year 1 and 2 • Number of new or enlarging T2 lesions at year 1 and 2 • Number of Gd+ lesions at year 1 and 2

DELIVER study[49]	Phase 1b, 32-week, multicentre, randomised, open-label, parallel group (complete)	US	RRMS or SPMS (n=76)	RRMS (n=24): • Natalizumab-TYS 300 mg IV (n=12) • Natalizumab-TYS 300 mg SC-PFS (n=12) SPMS (n=52): • Natalizumab-TYS 300 mg IV (n=16) • Natalizumab-TYS 300 mg SC (n=14) • Natalizumab-TYS 300 mg IM (n=15) • Natalizumab-TYS 300 mg RTC (n=7)	• Male/female age 18 to 65 with diagnosis of RRMS or SPMS • Natalizumab-TYS naïve • BMI 18 to 25 kg/m^2 • EDSS score 0.0 to 6.5 (patients with RRMS) • EDSS score between 2.5 and 6.5 (patients with SPMS)	Primary objective:[59] • PK/PD comparison of natalizumab-TYS 300 mg over 8 weeks after a single IV, IM or SC administration Secondary objective:[59] • PK, PD, safety, tolerability and immunogenicity over 24 weeks with repeated dosing every 4 weeks and efficacy measures (EDSS, MSFC, relapse rates, Gd+ lesions)
REFINE study[50]	Phase 2, 72-week (60-weeks randomised dose and 12 weeks open-label), multinational, multicentre, randomised, blinded, dose-ranging (complete)	Belgium, France, Germany, Italy and Spain	RRMS (n=290)	• Natalizumab-TYS 300 mg IV Q4W (n=54) • Natalizumab-TYS 300 mg SC Q4W (n=45) • Natalizumab-TYS 300 mg IV Q12W (n=52) • Natalizumab-TYS 300 mg SC Q12W (n=54) • Natalizumab-TYS 150 mg IV Q12W (n=47) • Natalizumab-TYS 150 mg SC Q12W (n=38)	• Male/female age 18 to 55 diagnosis of clinically stable RRMS • Free of MS relapse for 12 months prior to randomisation • Previously treated with natalizumab-TYS 300 mg IV ≥11 months during 12 months prior to randomisation • Experienced ≥2 documented clinical relapses or 1 relapse and ≥1 Gd+ lesion during 12 months prior	Primary outcome: • Cumulative number of combined unique active lesions on MRI Exploratory outcomes: • ARR at week 60 • Proportion of patients relapsed by week 60 • Proportion of patients with 12-week CDW • Change in EDSS score from baseline score to week 60 Other assessments: • PK/PD assessments baseline to week 60 and safety at week 60

					to initiating natalizumab-TYS	
NOVA study[30]	Phase 3b, 72-week, multinational, multicentre, randomised, controlled, open-label rater-blinded (complete)	Americas, Europe (including UK), Western Pacific	RRMS (n=499)	• Natalizumab-TYS 300 mg IV Q4W (n=248) • Natalizumab-TYS 300 mg IV Q6W (n=251)	• Male/female age 18 to 60 diagnosis of RRMS • EDSS score ≤5.0 at screening • No relapses in the 12 months before randomisation • Received ≥11 doses of natalizumab-TYS 300 mg IV Q4W) for ≥12 months before randomisation with no missed doses in the previous 3 months	Primary outcome: • Number of new or newly enlarging T2 hyperintense lesions at week 72 Secondary outcomes: • Time to first relapse • ARR at week 72 • Time to 24-week CDI • Number of new Gd+ and T1 hypointense lesions at week 24, 38 and 72 • Number of new ore enlarging T2 lesions at week 24 and 48 • Safety Exploratory outcome: • Proportion of participants with no evidence of disease activity at week 72

Abbreviations: ARR, annualised relapse rate; BMI, body mass index; CDI, confirmed disability improvement; CDW, confirmed disability worsening; EDSS, Expanded Disability Status Scale; Gd+, gadolinium-enhancing; IM, intramuscular; IV, intravenous; MRI, magnetic resonance imaging; MSFC, Multiple Sclerosis Functional Composite; Natalizumab-TYS, natalizumab (Tysabri®); PD, pharmacodynamics; PFS, prefilled syringe; PK, pharmacokinetics; RRMS; relapsing–remitting multiple sclerosis; Q4W every 4 weeks; Q6W, every 6 weeks; Q12W, every 12 weeks; SC, subcutaneous; RTC, reference treatment control; SPMS, secondary progressive multiple sclerosis; UK, United Kingdom; United States

* Higher scores = higher disability

Source: Foley et al. (2022)[30]; Trojano et al. (2023)[45]; Nicholas et al. (2023)[46]; Plavina et al. (2016)[49]; Trojano et al. (2021)[50]; Polman et al. (2006)[47]; Hutchinson et al. (2009)[48]; Butzkueven et al. (2020)[59]

B.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

B.2.4.1 TOP study

The population in the effectiveness and safety 15-year final analysis included patients who had received ≥1 dose of natalizumab-TYS, met study inclusion criteria and had provided informed consent.[59]

A *post-hoc* subgroup analysis of the TOP study of patients who had received prior treatment with ≥1 DMT and had experienced 1 relapse (n=[redacted]) was also conducted to determine the mean ARR pre- and post-natalizumab-TYS treatment (Section B.2.5.2).[51] The patient population in the subgroup analysis is the population most closely aligned to the population of interest for this appraisal (i.e. patients with highly active disease despite a full and adequate course of treatment with ≥1 DMT).

B.2.5 Clinical effectiveness results of the relevant trials

B.2.5.1 TOP study: 15-year final analysis (global and UK populations)

B.2.5.1.1 Patient disposition

A summary of patient disposition data for the TOP 15-year final analysis for the UK and global populations is provided in Table 7. As of November 2022, 134 of the 6,321 patients who were enrolled globally in the TOP study were from the UK (Table 7).[45]

A total of 83 patients ([redacted]%) and 3,993 patients (63.2%) discontinued natalizumab-TYS in the UK and global populations, respectively (Table 7).[45, 61] The most common reason for treatment discontinuation was [redacted] and (1,932 patients, 30.6%) in the UK and global populations, respectively.[45, 61]

Table 7: Patient disposition: 15-year final analysis, UK and global populations

Patients disposition	UK population	Global populations
Enrolled, n	134*	6,321*
Discontinued natalizumab-TYS, n (%)	[redacted]	3,993 (63.2)
Discontinued natalizumab-TYS but remained in TOP, n (%)	[redacted]	1,272 (20.1)
Withdrew from TOP, n (%)	[redacted]	2,721 (43.0)

Abbreviations: n, number; natalizumab-TYS, natalizumab (Tysabri®); TOP, Tysabri Observational Program
* As of 1 November 2022
Source: Trojano et al. (2023)[45]; Nicholas et al. (2023)[46]; Biogen Data on File[61]

B.2.5.1.2 Baseline demographics and clinical characteristics

A summary of baseline demographics and clinical characteristics for the 15-year analysis is provided in Table 8.

At baseline, there was a higher proportion of patients with EDSS score ≥3.0 (79.0% vs. 63.7%), a shorter median disease duration (6.0 vs. 8.0 years), and a shorter duration of prior DMT use (median 1.0 vs. 2.6 years) in the UK population vs. the global population, respectively (Table 8).[46] This data suggests that the UK population had a more aggressive disease course than patients in the global population.[46] Furthermore, 72.4% of the UK population had ≥1 prior DMT.[46] In the global population, 92.6% of patients had ≥1 prior DMT.[45]

Table 8: Baseline demographics and clinical characteristics: 15-year final analysis, UK and global populations

Characteristic	UK population N=134	Global population N=6,321
Age at baseline, mean (SD), years	39.6 (8.9)	37.6 (9.8)
Female, n (%)	108 (80.6)	4,563 (72.2)
Relapses in year prior to natalizumab-TYS initiation, mean (SD)	2.2 (1.1)	2.0 (1.0)
Baseline EDSS score, mean (SD)	4.3 (1.7)*	3.5 (1.6)†
<3.0, n (%)	26 (21.0)	2,252 (36.3)
≥3.0, n (%)	98 (79.0)	3,947 (63.7)
Disease duration at baseline, median (range), years	6.0 (1.0 to 27.0)	8.0 (1.0 to 44.0)
Patients with DMT use prior to natalizumab-TYS, n (%)	97 (72.4)	5,854 (92.6)
Prior DMTs, n (%)		
0	[redacted]	467 (7.4)
1	[redacted]	2,490 (39.4)
≥2	[redacted]	3,364 (53.2)
DMT duration prior to natalizumab-TYS initiation, years		
Median (range)	1.0 (0 to 11.3)	2.6 (0 to 39.0)‡

Abbreviations: DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; JCV, John Cunningham virus; Natalizumab-TYS, natalizumab (Tysabri®); n, number; SD, standard deviation
* n=124, baseline EDSS data were missing for 10 patients
† n=6,199, baseline EDSS data were missing for 122 patients
‡ Maximum value represents 1 patient who received chronic systemic corticosteroids from 1977 to 2016
Source: Trojano et al. (2023)[45]; Nicholas et al. (2023)[46]; Biogen Data on File[61]

B.2.5.1.3 Relapses

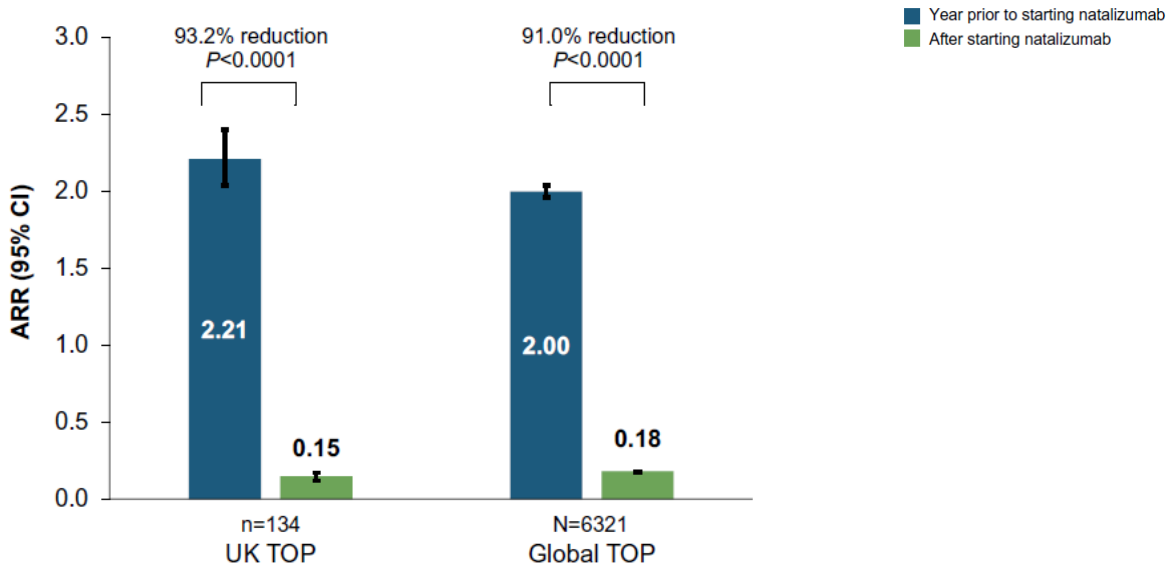
In the TOP study, ARRs were analysed using a Poisson model with robust variance error.[59]

Clinical relapses were defined as new or recurrent neurological symptoms not associated with fever lasting for ≥24 hours and followed by 30 days of stability or improvement.[59] Relapses were recorded up to 84 days after the last dose of natalizumab-TYS.[59] New or recurrent neurological symptoms that occurred <30 days after the onset of a protocol-defined relapse were considered part of the same relapse.[59]

Results from the 15-year final analysis were consistent with the 10-year interim analysis reinforcing the effectiveness of natalizumab-TYS over 15 years.

In the UK and global populations at 15 years significant annualised relapse rate (ARR) reductions were observed with natalizumab-TYS treatment (93.2% and 91.0%, respectively [p<0.0001 for both]) compared to the year prior to natalizumab initiation (Figure 5).[46] In the UK population the mean ARR decreased from 2.21 in the year prior to natalizumab-TYS treatment to 0.15 on natalizumab-TYS consistent with a decrease from 2.00 to 0.18 in the global population (Figure 5).[46]

Figure 5: Annualised relapse rate in the year before starting natalizumab-TYS treatment and after* natalizumab-TYS treatment: 15-year final analysis (UK and global populations)



Abbreviations: ARR, annualised relapse rate; CI, confidence interval; natalizumab-TYS, natalizumab (Tysabri®); n, number; TOP, Tysabri Observational Program
* Median (range follow-up: UK population, 11.2 (0.1 to 13.5 years); global population, 9.7 (0.0 to 16.7) years.
ARR reductions based on a comparison of the mean ARR across patients before and after initiation.
P values based on a repeated Poisson model accounting for in-person differences.
Source: Nicholas et al. (2023)[46]

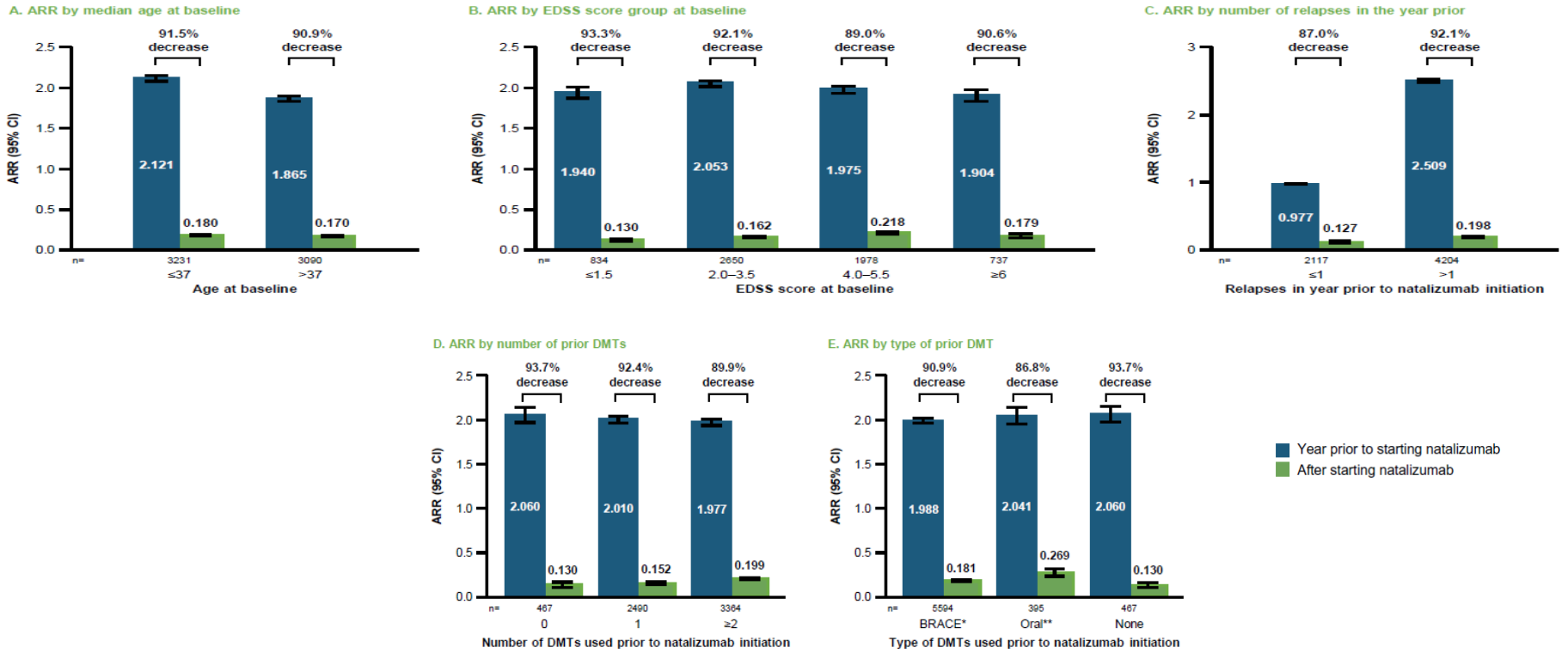
In the global population, significant ARR reductions were observed, with on-natalizumab-TYS treatment regardless of baseline age, baseline EDSS score, number of relapses in the year prior to natalizumab-TYS, number of prior DMTs and type of prior DMT.[45] The on-treatment ARR reductions ranged from 86.8% to 93.7% (Figure 6).[45]

During treatment with natalizumab-TYS most patients in the global population were relapse-free (n=3,719; 58.8%).[45] The estimated cumulative probability of remaining relapse-free over 15 years was 42.5%.[45]

In the UK population, significant ARR reductions were also observed regardless of EDSS score and prior number of DMTs. The ARR decreased by 95.0% and 93.4% for patients with baseline EDSS score <3.0 and ≥3.0, respectively (p<0.0001 for both).[46] The ARR decreased

by 93.2%, 93.4% and 94.7% in patients with no prior DMT, 1 prior DMT and ≥2 prior DMTs, respectively ($p<0.0001$ for all).[46]

Figure 6: Annualised relapse rate in the year before starting natalizumab-TYS treatment and after natalizumab-TYS treatment by (A) age at baseline, (B) EDSS score at baseline, (C) number of relapses in the year prior, (D) number of prior DMTs and (E) type of prior DMT: 15-year final analysis (global population)



Abbreviations: ARR, annualised relapse rate; CI, confidence interval; DMT, disease-modifying therapy; EDSS Expanded Disability Status Scale; natalizumab-TYS, natalizumab (Tysabri®)
* BRACE=Betaseron®, Rebif®, Avonex®, Copaxone®, Extavia®
** Oral=fingolimod, teriflunomide, tecfidera. A patient could have >1 DMT.
Source: Trojano et al. (2023)[45]

B.2.5.1.4 TOP study: Disability progression

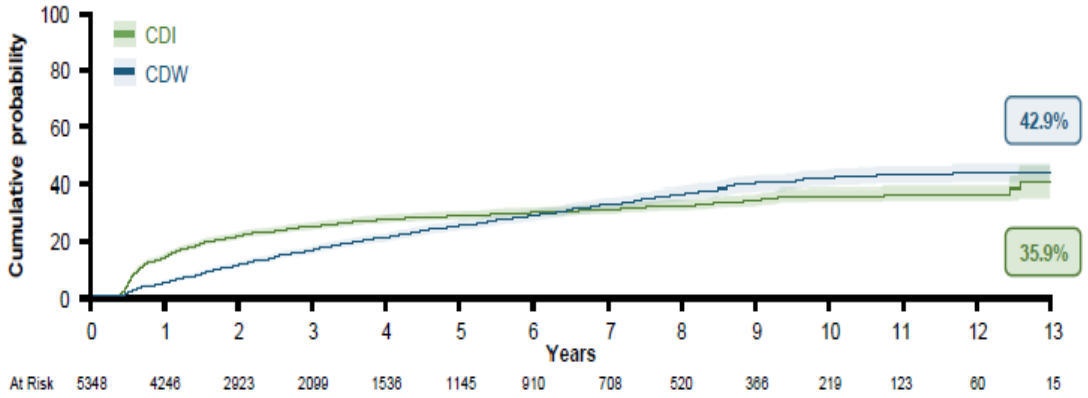
The Kaplan-Meier method was used to estimate the cumulative probabilities of CDW often referred to as confirmed disability progression (CDP) and the cumulative probabilities of CDI.[59]

In the TOP study CDW was defined as an increase, confirmed 24 weeks later, of ≥0.5 point from a baseline EDSS score of ≥6.0, ≥1.0 point from a baseline EDSS score of ≥1.0 to <6.0 or ≥1.5 points from a baseline EDSS score of 0.0.[59] CDI was defined as a decrease, confirmed 24 week later, of ≥1.0 point from a baseline EDSS score of ≥2.0.[59] Confirmation of 24-week CDW or CDI could occur up to 84 days after the last dose of natalizumab-TYS.[59]

In the global population at 15 years, the cumulative probability of CDW and CDI were 42.9% and 39.6%, respectively (the number of patients at risk after 13 years was low).[45] At 13 years, the cumulative probabilities of CDW and CDI were 42.9% and 35.9%, respectively (Figure 7).[45]

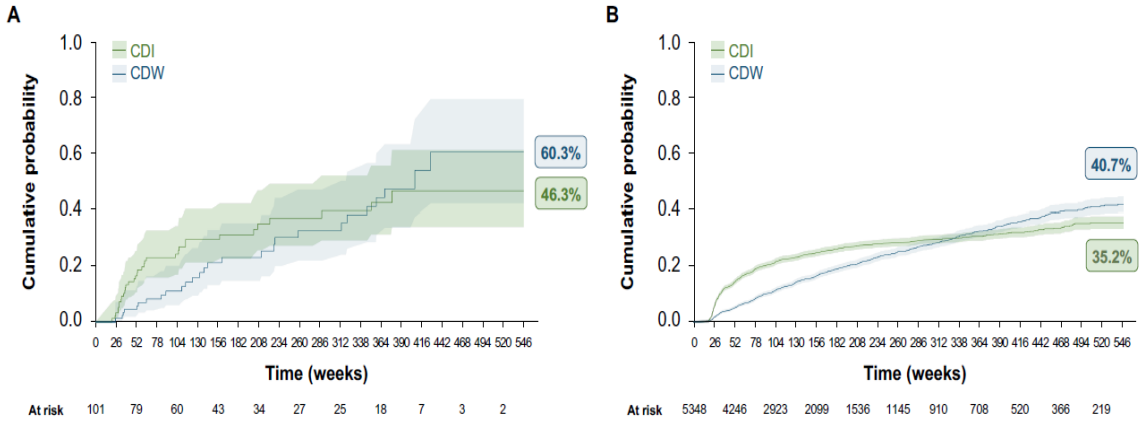
At 10.5 years the cumulative probability of CDW and CDI was 60.3% and 46.3% in the UK population, respectively and 40.7% and 35.2% in the global population, respectively (Figure 8).[46]

Figure 7: Estimated cumulative probability of 24-week CDW and 24-week CDI at 13 years in the global population: 15-year final analysis



Abbreviations: CDI, confirmed disability improvement; CDW, confirmed disability worsening; EDSS, Expanded Disability Status Score
Eligibility for CDW: Patients had to have non-missing baseline EDSS and 2 follow-up EDSS assessments
Eligibility for CDI: Patients had to have a baseline EDSS score ≥2 plus at least 2 follow-up EDSS assessments
Source: Nicholas et al. (2023)[46]

Figure 8: Estimated cumulative probability of 24-week CDW and 24-week CDI at 10.5 years in the (A) UK and (B) global population: 15-year final analysis



Abbreviations: CDI, confirmed disability improvement; CDW, confirmed disability worsening; EDSS, Expanded Disability Status Score
Eligibility for CDW: Patients had to have non-missing baseline EDSS and 2 follow-up EDSS assessments
Eligibility for confirmed disability improvement: Patients had to have non-missing baseline EDSS, 2 follow-up EDSS assessments, and baseline EDSS score ≥2
Source: Nicholas et al. (2023)[46]

B.2.5.2 Subgroup analysis

A *post-hoc* subgroup analysis of the TOP study of patients who had received prior treatment with ≥1 DMT and had experienced 1 relapse (n=[redacted]) was conducted to determine the mean ARR pre- and post-natalizumab-TYS treatment.[51] The patient population in the subgroup analysis is the population most closely aligned to the population of interest for this appraisal (i.e. patients with highly active disease despite a full and adequate course of treatment with ≥1 DMT).

The mean ARR decreased from [redacted] pre-natalizumab-TYS to [redacted] post-natalizumab-TYS treatment (Table 9) demonstrating that regardless of 1 relapse in the prior year and prior DMT use, natalizumab-TYS reduces the risk of relapse.[51]

Table 9: Summary of mean ARR pre- and post-natalizumab-TYS treatment in the subgroup of patients who have had ≥1 prior DMT and have experienced a relapse in the TOP study

	Pre-natalizumab-TYS (n=1,854)	Post-natalizumab-TYS (n=1,854)
Patients with relapse, n (%)	[redacted]	[redacted]
Total relapses, n	[redacted]	[redacted]
Mean ARR (95% CI)	[redacted]	[redacted]

Abbreviations: ARR, annualised relapse rate; CI, confidence interval; DMT, disease-modifying therapy; n, number; natalizumab-TYS, natalizumab (Tysabri®); TOP, Tysabri® Observational Program
Source: Biogen Data on File[51]

DMT use prior to natalizumab-TYS treatment for the [redacted] patients included in the *post-hoc* subgroup analysis of the TOP study is provided in Table 10.

Table 10: DMT use in the subgroup of patients from the TOP study prior to natalizumab-TYS treatment

DMT	Ever used
Treatment for MS – DMT n/N (%)	[redacted]
Alemtuzumab (Lemtrada), n (%)	
Daclizumab, n (%)	
Dimethyl fumarate, n (%)	
Fingolimod (Gilenya), n (%)	
Glatiramer acetate (Copaxone), n (%)	
Interferon, n (%)	
Interferon Alpha, n (%)	
Interferon beta-1a (Avonex), n (%)	
Interferon beta-1a (Rebif), n (%)	
Interferon beta-1b (Betaferon/Betaseron/Extavia), n (%)	
Natalizumab-TYS, n (%)	
Ocrelizumab, n (%)	
Rituximab (Rituxan), n (%)	
Teriflunomide, n (%)	

Abbreviations: DMT, disease-modifying therapy; MS, multiple sclerosis, n, number; natalizumab-TYS, natalizumab (Tysabri®); TOP, Tysabri® Observational Program
Source: Biogen Data on File[51]

B.2.5.3 Supportive studies

B.2.5.3.1 Efficacy and safety of natalizumab-TYS in patients with RRMS

Efficacy and safety of natalizumab-TYS IV in patients with RRMS

AFFIRM study[47, 48]

- The pivotal phase 3, double-blind RCT (AFFIRM) demonstrated the efficacy and safety of natalizumab-TYS vs. placebo over 2 years in patients with RRMS
- Natalizumab-TYS significantly reduced clinical relapses, disability progression and the formation of lesions (visualised by MRI) over 2 years vs. placebo in the overall population
- In the subgroup of patients with high disease activity (equivalent to RES patients) natalizumab-TYS significantly reduced clinical relapses and disability progression vs. placebo
- Natalizumab-TYS had an excellent safety and tolerability profile

AFFIRM study (IV formulation, RRMS [including highly active] population)

The AFFIRM study was a Phase 3, 2-year, double-blind, randomised, study of patients with RRMS who had experienced ≥1 relapse during the year prior to entry.[47, 48] Patients received either natalizumab-TYS 300 mg IV (n=627; n=148 with high disease activity [equivalent to RES patients]) or placebo (n=315; n=61 with high disease activity [equivalent to RES patients]) every 4 weeks.[47, 48]

Relapses

Natalizumab-TYS patients had a 68% relative reduction in the ARR after 2 years vs. placebo (p<0.001).[47] In addition, over 2 years, natalizumab-TYS reduced the risk of relapse by 59% (p<0.001).[47] The proportion of relapse-free patients was significantly higher with natalizumab-TYS vs. placebo at year 1 (77% vs. 56%, p<0.001, respectively) and 2 years (67% vs. 41%, p<0.001).[47]

In a *post hoc* subgroup analysis natalizumab-TYS patients with high disease activity (equivalent to RES patients) had higher baseline activity as compared to the overall population; these patients had a reduction in ARR by 81% compared with placebo (0.28 vs 1.46, respectively, p<0.001).[43]

Disability progression

Natalizumab-TYS was associated with a 42% reduction in the risk of EDSS disability progression sustained for 3 months over 2 years vs. placebo (p<0.001).[47] When disability progression sustained for 6 months was considered, there was a 54% reduction in the risk of progression of disability with natalizumab-TYS vs. placebo (p<0.001).[47] In addition, 83% of natalizumab-TYS patients had no sustained disability progression at 2 years vs. 71% of placebo patients (p<0.001).[47]

The mean 2-year cumulative probability of disability progression sustained over 3 months was also reduced in the subgroup of patients with high disease activity (equivalent to RES patients), by 53% compared with placebo (14% vs 29%, respectively; p=0.029).[43] When disability progression sustained over 6 months was considered, the risk was reduced by 64% vs. placebo (p=0.008).[43]

T2 lesions and gadolinium-enhanced lesions

Natalizumab-TYS significantly reduced patients' brain and CNS lesion burden in AFFIRM. Compared with placebo after 2 years:

- An 83% reduction in the mean number of new or enlarging T2 hyperintense lesions (1.9 vs. 11.0, respectively; p<0.001)[47]
- No new or enlarging T2 hyperintense lesions were seen in 57% of patients in the natalizumab-TYS group vs. 15% of patients in the placebo group (p<0.001)[47]
- A 76% decrease in new T1-hypointense lesions (1.1 vs. 4.6; p<0.001)[1, 2]
- A 92% reduction in the mean number Gd+ lesions vs. placebo (0.1 vs. 1.2; p<0.001)[47]

Safety

The incidence of common adverse events (AEs) was similar between the natalizumab-TYS group and the placebo group. The most common AEs for natalizumab-TYS and placebo patients, respectively, were headache (38% vs 33%), fatigue (27% vs 21%), urinary tract infection (20% vs 17%), arthralgia (19% vs 14%), and depression (19% vs 16%).[47] AEs that were significantly more common in the natalizumab-TYS group were fatigue and allergic reaction.[47] Common AEs were generally mild and resolved with continued therapy. Natalizumab-TYS was associated with a low rate of discontinuation due to AEs (6% for natalizumab-TYS vs 4% for placebo).[47]

SAEs occurred at a similar rate between groups; 19% for natalizumab-TYS, 24% for placebo (p=0.06).[47] The most frequent SAEs with natalizumab-TYS (vs placebo) were multiple sclerosis relapses (6% vs 13%, p<0.001), cholelithiasis (<1% for both) and the need for rehabilitation therapy (<1% for both).[47]

B.2.5.3.2 Pharmacokinetic/pharmacodynamic parameters, efficacy and safety of natalizumab-TYS SC

Pharmacokinetic (PK)/pharmacodynamic (PD) parameters, efficacy and safety of natalizumab-TYS SC

DELIVER and REFINE studies[49, 50]

- The DELIVER study demonstrated the PK and PD parameters of natalizumab-TYS SC route of administration are comparable to those of the IV route
- The REFINE study demonstrated comparable efficacy (MRI and relapses) between natalizumab-TYS SC and natalizumab-TYS IV
- Overall, the safety profile of natalizumab-TYS SC in both studies was consistent with the well-established safety profile of natalizumab-TYS IV

DELIVER study (subcutaneous formulation natalizumab-TYS naïve population)

DELIVER was a Phase 1b, 32-week randomised, open-label parallel group study in patients with RRMS (n=24) and SPMS (n=52) and who were natalizumab-TYS naïve. Patients received natalizumab-TYS 300 mg IV, natalizumab-TYS 300 mg SC or natalizumab-TYS 300 mg intramuscular (IM). PK and PD were evaluated over 8 weeks after the first natalizumab-TYS treatment (Part 1) and over 24 weeks with repeated dosing every 4 weeks, beginning at week 8 (Part 2).[49]

Pharmacokinetic and pharmacodynamic

No apparent differences were observed in PK parameters between patients with SPMS and RRMS; therefore, the SPMS and RRMS groups were combined for each route of administration. The impact on PK was observed via the mean serum concentration of natalizumab-TYS over time for the combined IV and SC group. The PK parameters (Cmax and Tmax) differed between SC and IV administration routes after the first dose but were similar between groups after repeated dosing.[49] Natalizumab-TYS 300 mg SC Q4W resulted in α4-integrin saturation comparable to natalizumab-TYS 300 mg IV Q4W.[49] Due to the exploratory nature of the study, no formal efficacy evaluations were made.[49]

Safety

There were no meaningful differences in the incidence of AEs, SAEs, administration site reactions, hypersensitivity reactions or anti-natalizumab-TYS antibodies between the administration groups.[49]

REFINE study (subcutaneous formulation, pre-treated with natalizumab-TYS IV for ≥12 months population)

REFINE was a Phase 2, 72-week (60-weeks randomised dose and 12 weeks open-label), multinational, multicentre, randomised, blinded, dose-ranging study in patients with RRMS

(n=290).[50] Patients received either natalizumab-TYS 300 mg IV or SC Q4W, natalizumab-TYS 300 mg IV or SC Q12W or natalizumab-TYS 150 mg IV or SC Q12W.[50]

Pharmacokinetic and pharmacodynamic

The impact on PK was observed via the mean trough serum natalizumab-TYS concentration over time for the individual groups. Natalizumab-TYS 300 mg SC Q4W treatment group showed comparable trough concentrations compared with the 300 mg IV Q4W treatment group.[50] Natalizumab-TYS 300 mg SC Q4W resulted in α4-integrin saturation comparable to natalizumab-TYS 300 mg IV Q4W.[50]

Efficacy

In terms of efficacy, natalizumab-TYS 300 mg IV and natalizumab-TYS 300 mg SC were comparable. The mean cumulative number of combined unique active MRI lesions was 0.23 and 0.02 for the natalizumab-TYS 300 mg IV Q4W treatment group and the natalizumab-TYS 300 mg SC Q4W treatment group, respectively.[50] ARRs were 0.07 and 0.08 in the natalizumab-TYS 300 mg IV Q4W and natalizumab-TYS 300 mg SC Q4W groups, respectively.[50]

Safety

Incidence of the most common treatment-related AEs and SAEs were consistently low in the natalizumab-TYS 300 mg IV Q4W and the natalizumab-TYS 300 mg SC Q4W groups.[50] No evidence for immunogenicity was observed in either group.[50] One case of PML was reported in the natalizumab-TYS 300 mg IV Q4W treatment group (in the context of long-term administration of natalizumab-TYS prior to study entry).[50]

B.2.5.3.3 Efficacy and safety of switching from natalizumab-TYS IV to natalizumab-TYS SC

Efficacy and safety of switching from natalizumab-TYS IV to natalizumab-TYS SC

Analysis of the TOP study[52]

- Based on an analysis of the TOP study efficacy and safety appear to be maintained in patients switching from natalizumab-TYS IV to natalizumab-TYS SC

Retrospective cohort study[53]

- [redacted]

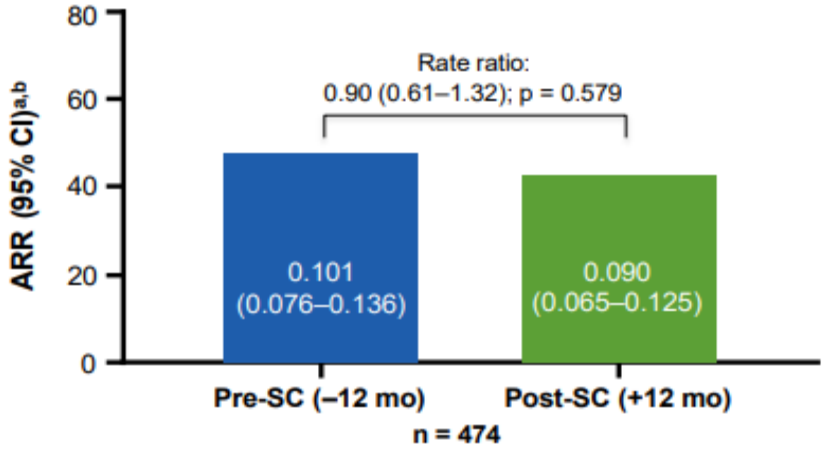
Analysis of the TOP study

Based on an analysis of the TOP study, efficacy and safety appear to be maintained in patients switching from natalizumab-TYS IV to natalizumab-TYS SC.[52] A total of 474 patients switched from natalizumab-TYS IV to natalizumab-TYS SC and remained on the SC regimen for ≥12 months.[52] Post switch the differences in the ARR pre-natalizumab-TYS SC and post-natalizumab-TYS SC (Figure 9), were not statistically significant (p=0.579).[52]

Furthermore, the differences in the EDSS increase were not statistically significant between pre-natalizumab-TYS SC (0.026) and post-natalizumab-TYS SC (0.069); p=0.196.[52]

A total of 14 SAEs occurred post-switch were identified from 13 patients (2.7%), none of the SAEs were related to natalizumab-TYS SC or MS relapse.[52]

Figure 9: ARR pre- and post-natalizumab-TYS SC



Abbreviations: ARR, annualised relapse rate; CI, confidence interval; natalizumab-TYS, natalizumab (Tysabri®); SC, subcutaneous
Source: Kappos et al. (2024)[52]

Retrospective cohort study

[redacted][53]

B.2.5.3.1 Efficacy and safety of natalizumab-TYS IV SID vs. natalizumab-TYS IV EID

Efficacy and safety of natalizumab-TYS IV SID vs. natalizumab-TYS IV EID

NOVA study[30]

- The NOVA phase 3b study (Part 1) demonstrated that patients who receive natalizumab-TYS IV SID (Q4W) can switch to natalizumab-TYS IV EID (Q6W) without any meaningful loss of efficacy and safety

SLR and meta-analysis[54]

- A recently published meta-analysis supports the results from the NOVA phase 3b study (Part 1) reporting no significant differences in efficacy and safety between natalizumab-TYS SID and natalizumab-TYS EID

TOUCH programme safety database

In the updated analysis of the Tysabri® Outreach: Unified Commitment to Health (TOUCH) programme safety database (as of 30th June 2023) in the United States (US) natalizumab-TYS EID (Q6W) was associated with a significantly lower risk of PML vs. natalizumab-TYS SID (Q4W) over the entire study period:[63]

- Primary analysis: 87% (hazard ratio [HR] 95% CI=0.134 [0.064 to 0.279]; p<0.0001)
- Secondary analysis: 81% (HR [95% CI] 0.189 [0.106 to 0.337]; p<0.0001)
- Tertiary analysis: 96% (HR [95% CI] 0.035 [0.006 to 0.195]; p=0.0001)

NOVA study (Part 1)

Efficacy and safety of natalizumab-TYS 300 mg IV EID (Q6W) vs. natalizumab-TYS 300 mg IV SID (Q4W) was evaluated in the NOVA Phase 3b, 72-week, prospective, randomised open-label clinical study. In Part 1 of the study patients with RRMS received natalizumab-TYS 300 mg IV Q6W (n=251) or natalizumab-TYS 300 mg IV Q4W (n=248).[30]

Efficacy

Mean number of new or newly enlarging T2 hyperintense lesions at Week 72 were 0.20 (95% confidence interval [CI]: 0.07 to 0.63) and 0.05 (95% CI: 0.01 to 0.22) in the Q6W and Q4W groups, respectively.[30] The proportion of participants who developed new or newly enlarging T2 lesions, T1-hypotense lesions and Gd+ lesions were similar in both groups (4.3% vs. 4.1%), (1.2% vs. 0.8%), (0.4% vs. 0.4%), respectively.[64] There were no significant differences in ARR (p=0.63), time to first relapse (p=0.64), the proportion of participants free of 24-week CDW (p=0.40), and participants with no evidence of disease activity (NEDA), (p=0.52) at 72 weeks between the Q6W and Q4W groups.[30]

Safety

Safety findings were consistent with the known safety profile of natalizumab-TYS 300 mg IV Q4W.[30] The proportions of patients with AEs and SAEs were similar in the natalizumab-TYS 300 mg IV Q6W and the natalizumab-TYS IV Q4W groups.[30]

SLR and meta-analysis

A recently published SLR and meta-analysis (2024) assessing the efficacy and safety of natalizumab-TYS EID vs. SID, also found no significant differences in efficacy (clinical relapses, new or newly enlarging T2 hyperintense lesions, change in EDSS score), and safety (PML) between natalizumab-TYS EID (Q5W to Q8W) and natalizumab-TYS SID.[54]

B.2.5.3.1 Efficacy and safety of natalizumab-TYS SC EID

Efficacy and safety of natalizumab-TYS SC EID

NOVA study (Part 2)[55]

- Disease activity was low during the crossover period when patients on natalizumab-TYS EID switched between the SC and IV formulations
- The incidence of AEs and SAEs were similar between the natalizumab-TYS SC and IV formulations and there were events of PML

Analysis of the TOP study[52]

- Efficacy and safety of natalizumab-TYS appears to be maintained in patients switching from natalizumab-TYS IV to natalizumab-TYS SC regardless of SID or EID dosing

NOVA study Part 2

Although Part 1 of the NOVA study was conducted in patients receiving natalizumab-TYS 300 mg IV EID there is no reason to expect that efficacy and safety of natalizumab-TYS SC EID would differ given the comparable PD and PK parameters, and efficacy and safety findings of natalizumab-TYS 300 mg SC and natalizumab-TYS 300 mg IV in the DELIVER and REFINE studies. Patients who completed Part 1 of the NOVA study were eligible to enter the NOVA extension study (Part 2).[55] In addition to these patients, enrolment was open to new patients.[55]

In Part 2, patients received natalizumab-TYS 300 mg IV Q6W for 36 weeks and were randomised to 48 weeks of crossover treatment comprising 24 weeks of natalizumab-TYS 300 mg SC Q6W and 24 weeks of natalizumab-TYS 300 mg IV Q6W, or vice-versa.[55] Secondary endpoints included number of new relapses, number of new or newly enlarged T2 lesions, number of new T1 lesions, number of Gd+ lesions and AEs.[55]

In total 153 patients were randomised in Part 2 including 86 new patients.[55] Of these, 141 patients were dosed (75 patients IV/SC and 66 patients SC/IV).[55]

Eight patients relapsed during NOVA Part 2 (5 patients IV/SC; 3 patients SC/IV), 7 patients relapsed in the 36-week run-in period but were not associated with MRI disease activity; 5 of 7 patients remained in the study without further disease activity.[55] A high percentage of patients were relapse-free 93.3% IV/SC and 95.5% SC/IV.[55] During the crossover period:[55]

- One patient missed a dose while on natalizumab-TYS SC Q6W and subsequently experienced a relapse and a new/newly enlarged T2 lesion
- The number of new/newly enlarged T2 lesions and T1 lesions were low, T2 lesions were observed in 2 patients after 24 weeks of SC Q6W dosing and 1 patient after IV Q6W dosing. One patient experienced a T1 lesion receiving IV Q6W dosing from baseline to 24 weeks
- No Gd+ lesions were observed

The incidence of AEs (62.1%; 57.4%) and related SAEs (0.8%; 0.0%) were similar between IV Q6W and SC Q6W groups.[55]

There were no events of PML, no development of anti-drug antibodies, no immunogenicity events and no deaths.[55] On switching to natalizumab-TYS SC, the incidence of injection site reactions was consistent with previous studies (DELIVER and REFINE).[55]

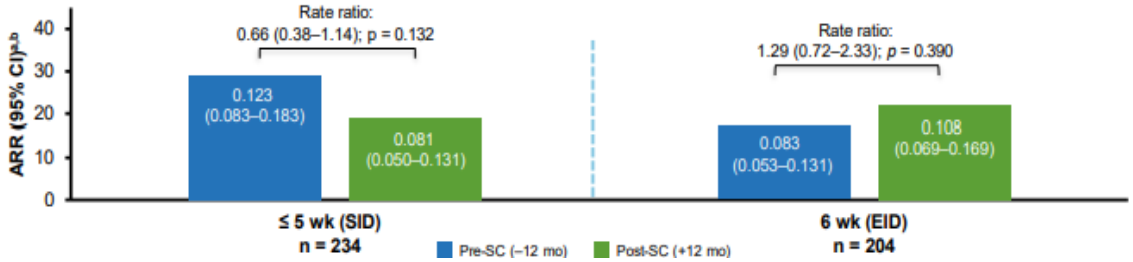
Analysis of the TOP study

In an analysis of the TOP study, efficacy and safety of natalizumab-TYS appears to be maintained in patients switching from natalizumab-TYS IV to natalizumab-TYS SC regardless of SID (≤Q5W) or EID (Q6W) dosing.[52]

In the SID (n=234) and EID (n=204) cohorts, differences in the ARR in the year prior and the year after the switch from natalizumab-TYS IV to natalizumab-TYS SC were not statistically significant (Figure 10).[52]

There were no statistically significant differences in EDSS score pre-SC and post-SC in the SID (p=0.240) and EID (p=0.411) cohorts.[52] Fewer SAEs were reported in patients post-natalizumab-TYS SC switch who were treated with EID vs. SID.[52]

Figure 10: Pre- and post-natalizumab-TYS SC ARR in the SID and EID cohorts



Abbreviations: ARR, annualised relapse rate; CI, confidence interval; EID, extended interval dosing; natalizumab-TYS, natalizumab (Tysabri®); SC, subcutaneous, SID, standard interval dosing
Source: Kappos et al. (2024)[52]

B.2.6 Benefits of natalizumab-TYS (Tysabri®) vs. natalizumab (Tyruko®)

Natalizumab-TYS is available as both an IV formulation and SC formulation, in contrast to natalizumab-TYR the SC formulation provides benefits to patients and the NHS

- The SC formulation of natalizumab-TYS allows for administration closer to home, in primary care centres, HCP offices, and other similar settings
- [redacted]
- Moving care closer to home, will help to address health inequalities a key priority outlined in the NHS Long Term Plan[42]
- The range of benefits provided by the natalizumab-TYS SC formulation compared with the IV formulation of natalizumab-TYS and natalizumab-TYR include:
    - Cost savings to the NHS (reduction in HCP time, chair time equipment costs [infusion sets])
    - Increased infusion suite capacity allowing more MS patients to be treated reducing waiting lists
    - Enhanced patient choice, convenience (reduced drug administration, observation and travel time), reduced personal expenditure (travel costs)
- A number of clinical (Phase 3b NOVA extension study) and prospective real-world studies have reported high levels of patient preference for natalizumab-TYS SC[55–58]
- To manage PML risk Biogen provides the StratifyJCV™ service free of charge

B.2.6.1 SC formulation

Natalizumab-TYS is available as both an IV formulation and SC formulation, in contrast to natalizumab-TYR which is only available as an IV formulation.

The IV formulation for natalizumab-TYS and natalizumab-TYR are administrated over a 1-hour infusion, typically in a tertiary infusion centre which can often be over an hour away from home, incurring time off work for those in employment and personal expenditure (travel costs). A 1-hour post-infusion observation is required for the first 12 infusions. After the first 12 infusions, if patients have not experienced any infusion reactions, the post dose observation time may be reduced or removed according to clinical judgement (SmPC Section 4.2).[1, 2]

A prospective, observational study (n=113) nested in the Trajectories of Outcome on Neurological Conditions (TONiC-MS) multicentre UK study, reported 39.8% of patients with MS travelled between 1 to 2 hours, 8% travelled 2 to 4 hours and 3.5% travelled over 4 hours for MS treatment administration.[56]

The SC formulation of natalizumab-TYS currently allows for administration closer to home, in primary care centres, HCP offices, and other similar settings.[1, 2] The SC formulation consists of two prefilled syringes administered consecutively within 30 minutes (expected to take less

than 5 minutes) and has a 1-hour post-injection observation time which may be reduced or removed according to clinical judgement after the first 6 doses.

National policy such as the Five Year Forward View[65] and the supporting New Care Models Programme (one of the first steps toward delivering the Five Year Forward View) have encouraged efforts to deliver more healthcare closer to home (from hospitals to primary/community care), with the aim of providing better healthcare for patients and reducing net costs. Moving care closer to home, will also help in addressing health inequalities a key priority outlined in the NHS Long Term Plan.[42]

The range of benefits provided by the natalizumab-TYS SC formulation compared with the IV formulation of natalizumab-TYS and natalizumab-TYR are outlined in Table 11.

[redacted]

Table 11: Range of benefits provided by the SC formulation of natalizumab-TYS

	Benefit
Patients/carers	• Enhanced patient choice • Convenience (reduced administration, observation and travel time) • Reduces personal expenditure (travel costs) • Addresses poor venous access • Alleviates the need to access infusion centre
HCPs	• Reduces preparation, administration and observation time • Supports routine patient management
NHS	• Reduces NHS costs (HCPs, chair time, equipment costs [infusion sets]) • Increased infusion suite capacity allowing more MS patients to be treated reducing waiting lists
[redacted]	[redacted]
National policy	• Brings care closer to home
Environment	• Potential for reduced waste for incineration[1, 2, 66] • Zero electricity requirement for administration vs. infusion pumps[1, 2, 67] • Potential for reduced CO_2 emissions due to reduced travel time if SC is administered in a setting closer to home[1, 2, 68–70]

Abbreviations: CO_2, carbon dioxide; HCPs, healthcare professionals; MS, multiple sclerosis; NHS, National Health Service; natalizumab-TYS, natalizumab (Tysabri®); SC, subcutaneous

Time, resource and cost saving

An Excel® spreadsheet costing model was developed to calculate the time, resource and cost savings associated with switching patients from natalizumab-TYS IV to natalizumab-

TYS SC. Switching 500 patients from natalizumab-TYS IV to SC results in hospital chair time savings of [redacted], nurse/pharmacy time savings of [redacted] and total cost savings of [redacted] (Table 14).[71]

The drug administration assumptions and input costs for this scenario are provided in Table 12 and Table 13.

Table 12: Drug administration assumptions for natalizumab-TYS IV and SC

Dosing and observation	Natalizumab-TYS IV	Natalizumab-TYS SC
Average number of doses (per year)	[redacted]	[redacted]
Number of doses before observation can be reduced	[redacted]	[redacted]
Number of doses where reduced observation is possible in the first year of treatment	[redacted]	[redacted]
% of naïve patients eligible for reduced observation	[redacted]	[redacted]
% of experienced patients eligible for reduced observation	[redacted]	[redacted]
Administration time (minutes)	[redacted]	[redacted]
Observation time – naïve patients (minutes)	[redacted]	[redacted]
Observation time – experienced patients	[redacted]	[redacted]
Staffing and preparation	**Natalizumab-TYS IV**	**Natalizumab-TYS SC**
Number of patients per nurse*	[redacted]	[redacted]
Drug preparation time (nurse or pharmacy)	[redacted]	[redacted]

Abbreviations: IV, intravenous; natalizumab-TYS, natalizumab (Tysabri®); SC, subcutaneous
* The number of patients a nurse can manage at one time
Source: Biogen Data on File[71]; Natalizumab-TYS SmPC[1, 2]

Table 13: Drug acquisition, nursing/pharmacy and equipment costs per natalizumab-TYS IV and SC administration

Nursing/Pharmacy costs	Natalizumab-TYS IV	Natalizumab-TYS SC
Hourly rate*	[redacted]	[redacted]
Equipment costs (per administration))	**Natalizumab-TYS IV**	**Natalizumab-TYS SC**
0.9% normal saline 100 ml IV bag for flushing post-natalizumab-TYS	[redacted]	[redacted]
IV cannula	[redacted]	[redacted]
Posiflush (pre-filled saline syringe)	[redacted]	[redacted]
Needlefree extension	[redacted]	[redacted]
Gauze 5 x 5	[redacted]	[redacted]

IV giving set compatible with IV infusion pump	[redacted]	[redacted]
Single use tourniquets	[redacted]	[redacted]
2% chlorhexidine/70% alcohol applicator	[redacted]	[redacted]
IV dressing	[redacted]	[redacted]
20 ml syringe for drawing up natalizumab-TYS IV	[redacted]	[redacted]
Hypodermic needle for drawing up natalizumab-TYS IV	[redacted]	[redacted]
TOTAL	[redacted]	[redacted]

Abbreviations: IV, intravenous; natalizumab-TYS, natalizumab (Tysabri®); SC, subcutaneous
* All rates have been based on the first pay point for each band (NHS hourly pay 2021/2022)
Source: Biogen Data on File[71, 72]; NHS Pay[73]

Table 14: Time, resource and cost saving calculations, natalizumab-TYS IV vs natalizumab-TYS SC

	Current situation			Future scenario			Variance		
	Natalizumab-TYS IV (n=500)	Natalizumab-TYS SC (n=0)	Total	Natalizumab-TYS IV (n=0)	Natalizumab-TYS SC (n=500)	Total	Natalizumab-TYS IV	Natalizumab-TYS SC	Total
Time/year, hours									
Administration time/year, hours	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Observation time/year, hours	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TOTAL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nurse time/year, hours									
Patients/nurse, n	[redacted]	[redacted]		[redacted]	[redacted]		[redacted]	[redacted]	
Administration time/year, hours	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Observation time/year, hours	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TOTAL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nurse or pharmacy time/year, hours									
Preparation time	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Costs									
Administration costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Drug preparation costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Equipment costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TOTAL COSTS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: IV, intravenous; Natalizumab-TYS, natalizumab (Tysabri®); n, number; SC, subcutaneous
Source: Biogen data on file[71]

Time and motion studies

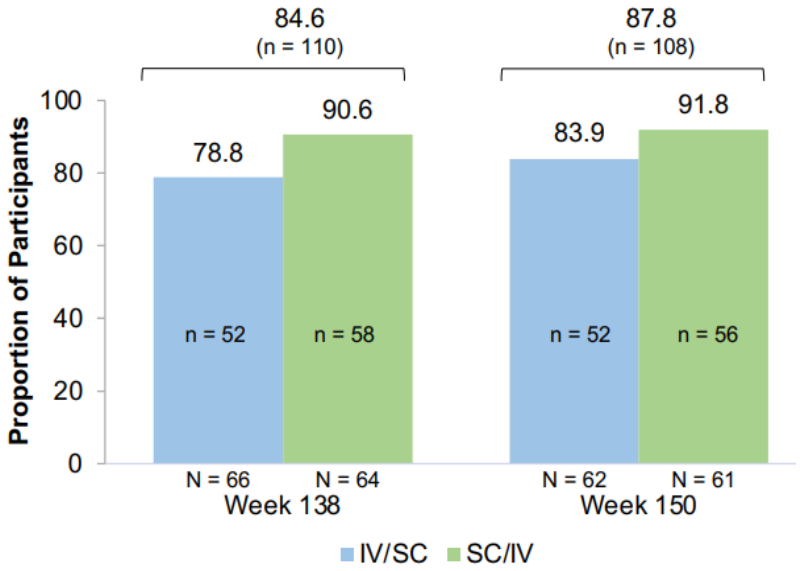
The time, resource and cost saving calculations are realised in clinical practice. A recent (2023) audit was conducted in the Brooke Treatment Unit (Salford), an outpatient department for the tertiary neurology service in Greater Manchester which provides DMT treatment for patients with MS.[74] One of the objectives of the audit was to evaluate the existing service provision for natalizumab-TYS and identify potential time savings associated with switching patients from natalizumab-TYS IV to natalizumab-TYS SC.[74] Natalizumab-TYS data was collected by direct observation of a statistically powered sample of 45 patients receiving natalizumab-TYS IV and 4 patients receiving natalizumab-TYS SC. Data was collected for the time spent from arrival at the unit for treatment until discharge. Results showed that natalizumab-TYS SC presents a viable option for reducing workload and increasing staff and chair time. Total time savings were 1 hour and 32 minutes for the natalizumab-TYS SC group vs. the natalizumab-TYS IV group.[74]

Patient preference

A number of studies have reported on patient preference for natalizumab-TYS SC vs. natalizumab-TYS IV.

The Phase 3b Nova extension study (Part 2) assessed patient preference for natalizumab-TYS SC vs. natalizumab-TYS IV.[55] Participants who completed the NOVA study (Part 1) were eligible for entry into Part 2 (n=67), in addition to new patients.[55] Patient preference questionnaires were administered during Weeks 138 and 150.[55, 75] At Week 138, 84.6% of participants preferred the SC route and at the end of the crossover period (Week 150) 87.8% of patients preferred the SC route (Figure 11).[55, 75]

Figure 11: Proportion of participants indicating preference for natalizumab-TYS SC at the end of the NOVA 3b extension study (Part 2)



Abbreviations: IV, intravenous; SC, subcutaneous
Source: Wiendl et al. (2023)[55] Wiendl et al. (2024)[75]

Patient preference questionnaires were administered prospectively in an observational study, nested in the Trajectories of Outcome on Neurological Conditions (TONiC-MS) multicentre UK study.[56] Of the 25 participants who switched to natalizumab-TYS SC, all except one patient expressed either a 'fairly strong' or 'very strong' preference over IV. Majority of reasons for switching were time savings.[56]

The ongoing observational, prospective SISTER study in Germany assessed patients' with RRMS preference for natalizumab-TYS SC vs. natalizumab-TYS IV.[57] In the interim analysis (up to February 2022), 90.5% (n=114) of patients chose natalizumab-TYS SC and 98.4% (n=121) patients stated they were satisfied with their choice.[57] The most frequent reason for preference of the SC route of administration were shorter duration of administration and convenience.[57]

In a questionnaire-based study conducted in Sweden (n=83) in patients with RRMS, 88% of patients preferred natalizumab-TYS SC vs. natalizumab-TYS IV from a time saving perspective.[58] In addition 75% of patients preferred to receive natalizumab-TYS SC in a primary care vs. hospital setting.[58] Natalizumab-TYS SC administration in primary care resulted in less interruption to work, 60% of patients indicated no impact on their work vs. 35% of patients who received natalizumab-TYS SC in a hospital setting.[58] Furthermore, 73% of patients on natalizumab-TYS SC spent less than 2 hours away work from work for treatment administration vs. 43% of patients on natalizumab-TYS IV.[58]

B.2.6.2 StratifyJCV™ service

To manage PML risk Biogen provides the StratifyJCV™ service free of charge (Stratify anti-JCV antibody assay test, CSF JCV DNA test and a PML risk stratification algorithm). StratifyJCV™ is for HCPs who are treating or intending to treat patients with natalizumab-TYS and not for HCPs who are treating or intending to treat patients with the natalizumab biosimilar (natalizumab-TYR).

The StratifyJCV™ PML risk stratification algorithm is based on a pooled patient cohort comprised of approximately 37,000 natalizumab-TYS treated patients who participated in natalizumab-TYS studies. The evidence for the risk stratification algorithm is specific to the StratifyJCV™ tests.

The provider of the tests in over 75 countries, including the UK, is Unilabs a leading company in diagnostics over 30 years. Unilabs' laboratories are accredited to the internationally recognised International Organization for Standardization (ISO) 15189 Medical Laboratories: Requirements for Quality and Competence standard. StratifyJCV™ is performed using a validated enzyme-linked immunosorbent assay (ELISA) and provides a numerical index which indicates the level of antibody in the patient. StratifyJCV™ has been shown to be consistent, sensitive, specific, and precise in a multi-site validation study and has a low false-negative rate of 2.2% to 3.0%.[76] Testing began in March 2011 and more than one million StratifyJCV™ tests have been conducted globally.[77]

The website https://stratifyjcv.unilabsweb.com/ is intended for HCPs registered for StratifyJCV™ and CSF JCV DNA testing. The website provides detailed information on how to order StratifyJCV™ kits, book courier pick-ups of blood samples, and view test results. The website is available for HCPs to register their patients for StratifyJCV™ or CSF tests.

With the implementation of risk estimates and patient management guidelines for HCPs, the incidence of PML among Tysabri®-treated patients has been stable with a downward trend since mid-2016. The global overall incidence of PML in natalizumab-TYS treated patients is 3.43 per 1,000 patients (95% confidence interval [CI]: 3.22 to 3.66 per 1, 000 patients), data cut-off date February 2024.[78]

B.2.7 Meta-analysis

B.2.7.1 Chappell et al. Literature review and meta-analyses of non-RCTs in patients with highly active RRMS

Full details of the methodology and results of the Chappell et al. meta-analyses of non-RCTs are provided in the Chappell et al. draft manuscript and Appendix D.[44]

The meta-analyses of the comparative studies included in the literature review (n=16) demonstrated statistically significant differences in favour of natalizumab-TYS vs. platform DMTs and the high-efficacy DMT, fingolimod.[44] Tabulated results of the meta-analyses are provided in the draft manuscript (Table 4 vs. platform DMTs and Table 5 vs. fingolimod).[44]

Specifically compared with fingolimod:[44]

- A significantly higher proportion of patients receiving natalizumab-TYS were relapse-free rate at 24-, 36- and 48-month follow-up ($p<0.05$)
- ARR was significantly lower for natalizumab-TYS-treated patients at 12 and 24 months ($p<0.001$)
- Natalizumab-TYS-treated patients had a significantly lower rate of 6-month CDP at 48 months follow-up ($p<0.001$)
- Natalizumab-TYS-treated patients had significantly higher rates of CDI for 3-, 6- and 12-month confirmation at 24 and 36 months ($p<0.01$)
- Rates of freedom from disease activity were significantly lower for patients receiving natalizumab-TYS at all time points ($p<0.0001$)
- Freedom from clinical and radiological disease activity was significantly more frequent for patients receiving natalizumab-TYS at 12-, 24-, and 48 months ($p<0.001$)
- Freedom from new Gd+ lesions and new T2 lesions was significantly greater for natalizumab-TYS-treated patients at 12 months ($p=0.01$)

There was a non-significant increase in the rate of treatment discontinuations at 24 months compared with fingolimod ($p=0.13$) and no significant differences in the rate of AEs for natalizumab-TYS compared to fingolimod.[44]

Additionally, in the case series (n=11) natalizumab-TYS was associated with high rates of freedom from relapse, clinical/radiological disease activity, reductions in ARR and disability progression.[44]

B.2.8 Adverse reactions

B.2.8.1 TOP study: 15-year final analysis (global population)

In the 15-year final analysis (UK and global population) there were no new safety signals and the incidence of opportunistic infections, PML and malignancies was low.[45]

B.2.8.1.1 Serious adverse events

In the UK population, [redacted] ([redacted]) patients experienced ≥1 SAE, of these [redacted] ([redacted]) patients had ≥1 treatment-related SAE.[61]

The most frequently reported SAEs by system organ class and MedRA preferred term were nervous system disorders [redacted] ([redacted]) patients; neoplasms benign, malignant and unspecified [redacted] ([redacted]) patients including malignancy incidence of [redacted] ([redacted]) patients; pregnancy, puerperium and perinatal conditions [redacted] ([redacted]) patients; infections and infestations [redacted] ([redacted]) patients including PML incidence of [redacted] ([redacted]) patients.[61]

In the global population, 17.8% (1,122 of 6,321) patients experienced ≥1 SAE, of these 4.7% (299 of 6,321) patients had ≥1 treatment-related SAE.[45]

The most frequently reported SAEs were PML and immune-reconstitution inflammatory syndrome (IRIS) each with an incidence of 0.9% (Table 15). The most frequently reported opportunistic infection and malignancy were PML and uterine leiomyoma, respectively.[45]

B.2.8.1.2 Deaths

There were [redacted] ([redacted]) and 49 (0.8%) deaths in the UK and global populations, respectively.[45, 61]

Table 15: Incidence of SAEs: 15-year final analysis (global population)

Event, n (%)	N=6,321
SAEs by MedDRA preferred term reported in ≥10 patients*	
PML, confirmed	53 (0.9)
IRIS	56 (0.9)
Abortion, spontaneous	49 (0.8)
Fall	29 (0.5)
Pneumonia	29 (0.5)
Multiple sclerosis relapse	27 (0.4)
Hypersensitivity	26 (0.4)
Urinary tract infection	23 (0.4)
Epilepsy	22 (0.3)
Herpes zoster	21 (0.3)
Depression	20 (0.3)
Appendicitis	16 (0.3)
Intervertebral disc protrusion	16 (0.3)
Uterine leiomyoma	15 (0.2)
Breast cancer	14 (0.2)
Cholelithiasis	14 (0.2)
Escherichia urinary tract infection	14 (0.2)

Pulmonary embolism	13 (0.2)
Back pain	12 (0.2)
Caesarean Section	11 (0.2)
Pyelonephritis	11 (0.2)
Suicide attempt	11 (0.2)

Abbreviations: IRIS, immune-reconstitution inflammatory syndrome; MedDRA, Medical Dictionary for Regulatory Activities; PML, progressive multifocal leukoencephalopathy, SAE, serious adverse event
* Each patient was only counted once within each preferred term. Multiple sclerosis was also reported as an SAE in 22 patients
Source: Trojano et al. (2023)[45]

B.2.9 Ongoing studies

There are no further ongoing studies for natalizumab-TYS for the treatment of patients with highly active RRMS beyond those described in prior sections.

B.3 Cost effectiveness

As agreed with NICE, Biogen are not submitting an economic model for this appraisal.

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Appendices

Appendix C: Summary of product characteristics (SmPC) and UK public assessment report

C.1 SmPC

Tysabri SmPC.pdf

C.2 UK public assessment report

Tysabri PAR.pdf

Appendix D: Identification, selection and synthesis of clinical evidence

D.1 Identification and selection of relevant studies

D.1.1 Search strategy

A targeted literature review was conducted in six key electronic databases in January 2023. The review was conducted outside of the NICE process. In the absence of RCTs for the highly active RRMS population the review was performed to address the evidence gap by identifying non-RCT evidence in the highly active RRMS patient population. The strategies comprised two concepts:

- RRMS (search lines 1 to 6)
- Natalizumab-TYS (search lines 7 to 11)

A MEDLINE (OvidSP) search strategy was designed to identify studies of natalizumab-TYS in RRMS. The final MEDLINE strategy is presented below (Source 1).

The strategy was devised using a combination of subject indexing terms and free text search terms in the Title, Abstract, Keyword Heading Word, Registry Number, Name of Substance and Original Title fields.

The search strategy was designed to retrieve studies reporting on the eligible RRMS population. To do this, the population terms in the strategy were designed to retrieve database records that referred to either non-specific MS or specific RRMS.

The database searches were conducted in the resources shown below (Sources 1 to 6). The selection of resources reflected the targeted literature review context.

Reflecting the eligibility criteria, Conference Proceedings Citation Index – Science (CPCI-S) search results and records indexed in Embase as conference abstracts were restricted to those published from 2020 to date. Reflecting the eligibility criteria, records indexed as preprints were excluded from the Embase search results.

Searches were conducted in each database, translating the agreed Ovid MEDLINE strategy appropriately. Translation included consideration of differences in database interfaces and functionality, in addition to variation in indexing languages and thesauri.

Translation reflected the targeted literature review context. A pragmatic approach was taken to two elements of the Embase translation. The Emtree subject heading for natalizumab was searched as a major descriptor. In addition, the natalizumab textword terms were not searched for in the CAS Registry Numbers field or the Drug Index Terms Word field. The pragmatic search approach was designed to reduce retrieved record numbers.

The final translated database strategies were peer-reviewed by a second Information Specialist. Peer review considered the appropriateness of the translation for the database being searched, errors in syntax and line combinations, and application of exclusions.

Source 1: MEDLINE ALL

Interface / URL: OvidSP

Database coverage dates: 1946 to 13 January 2023
Search date: 16 January 2023
Retrieved records: 2146
Search strategy:

1	Multiple Sclerosis/	61244
2	Multiple Sclerosis, Relapsing-Remitting/	7917
3	multiple scleros*.ti,ab,kf.	89016
4	(disseminated scleros* or sclerosis multiplex or insular scleros* or encephalomyelitis disseminata or chariot disease).ti,ab,kf.	784
5	(ms or rms or rrms).ti,ab,kf.	424233
6	or/1-5	471352
7	Natalizumab/	1891
8	natalizumab*.ti,ab,kf,rn,nm,ot.	3082
9	(an100226*2 or an-100226*2 or an100226m*2 or an-100226m*2 or antegran*2 or antegren*2 or bg0002*2 or bg-0002*2 or dst356a1*2 or dst-356a1*2 or pb006*2 or pb-006*2 or tysabri*2).ti,ab,kf,rn,nm,ot.	218
10	(189261-10-7 or 3jb47n2q2p).ti,ab,kf,rn,nm,ot.	1
11	or/7-10	3126
12	6 and 112579	
13	exp animals/ not humans/	5082768
14	(news or editorial or case reports).pt. or case report.ti.	3205196
15	12 not (13 or 14)	2146

Source 2: Embase

Interface / URL: OvidSP
Database coverage dates: 1974 to 13 January 2023
Search date: 16 January 2023
Retrieved records: 4151
Search strategy:

1	multiple sclerosis/	151991
2	multiple scleros*.ti,ab,kf,dq.	139071
3	(disseminated scleros* or sclerosis multiplex or insular scleros* or encephalomyelitis disseminata or chariot disease).ti,ab,kf,dq.	532
4	(ms or rms or rrms).ti,ab,kf,dq.	582349
5	or/1-4	658447
6	*natalizumab/	3537
7	natalizumab*.ti,ab,kf,dq,tn,ot.	6826
8	(an100226*2 or an-100226*2 or an100226m*2 or an-100226m*2 or antegran*2 or antegren*2 or bg0002*2 or bg-0002*2 or dst356a1*2 or dst-356a1*2 or pb006*2 or pb-006*2 or tysabri*2).ti,ab,kf,dq,tn,ot.	2049
9	(189261-10-7 or 3jb47n2q2p).ti,ab,kf,dq,tn,ot.	0

10 or/6-9 8219
11 5 and 107049
12 editorial.pt. or case report.ti. 1112425
13 (animal/ or animal experiment/ or animal model/ or animal tissue/ or nonhuman/) not exp human/ 6622486
14 preprint.pt. 49698
15 or/12-14 7746910
16 11 not 15 6790
17 conference abstract.pt. 4656030
18 16 and 17 3291
19 limit 18 to yr="2020 -Current" 652
20 16 not 17 3499
21 19 or 20 4151

Source 3: Cochrane Database of Systematic Reviews (CDSR)

Interface / URL: Cochrane Library / Wiley
Database coverage dates: Information not found. Issue searched: Issue 1 of 12, January 2023
Search date: 16 January 2023
Retrieved records: 11
Search strategy:

#1 [mh ^"multiple sclerosis"] 3220
#2 [mh ^"multiple sclerosis, relapsing-remitting"] 994
#3 multiple next scleros*:ti,ab,kw 11745
#4 (disseminated next scleros* or sclerosis next multiplex or insular next scleros* or encephalomyelitis next disseminata or chariot next disease):ti,ab,kw13
#5 (ms or rms or rrms):ti,ab,kw 23379
#6 #1 or #2 or #3 or #4 or #5 27347
#7 [mh ^"natalizumab"] 98
#8 natalizumab*:ti,ab,kw 453
#9 (an100226* or an-100226* or an100226m* or an-100226m* or antegran* or antegren* or bg0002* or bg-0002* or dst356a1* or dst-356a1* or pb006* or pb-006* or tysabri*):ti,ab,kw 71
#10 ("189261-10-7" or 3jb47n2q2p):ti,ab,kw 10
#11 #7 or #8 or #9 or #10 465
#12 #6 and #11 in Cochrane Reviews, Cochrane Protocols 11

Source 4: Cochrane Central Register of Controlled Trials (CENTRAL)

Interface / URL: Cochrane Library / Wiley
Database coverage dates: Information not found. Issue searched: Issue 1 of 12, January 2023
Search date: 17 January 2023
Retrieved records: 368
Search strategy:

#1 [mh ^"multiple sclerosis"] 3220
#2 [mh ^"multiple sclerosis, relapsing-remitting"] 994
#3 multiple next scleros* 12243
#4 (disseminated next scleros* or sclerosis next multiplex or insular next scleros* or encephalomyelitis next disseminata or chariot next disease) 17
#5 (ms or rms or rrms) 50847
#6 #1 or #2 or #3 or #4 or #5 53396
#7 [mh ^"natalizumab"] 98
#8 natalizumab* 493
#9 (an100226* or an next 100226* or an100226m* or an next 100226m* or antegran* or antegren* or bg0002* or bg next 0002* or dst356a1* or dst next 356a1 or pb006* or pb next 006* or tysabri*) 116
#10 ("189261-10-7" or 3jb47n2q2p) 10
#11 #7 or #8 or #9 or #10 535
#12 #6 and #11 in Trials 368

Source 5: HTA

Interface / URL: https://database.inahta.org/
Database coverage dates: Information not found
Search date: 17 January 2023
Retrieved records: 18
Search strategy:

Search terms were entered as below in the search box at the URL above. Line combinations were performed using the check boxes on the search history page.

1 multiple sclerosis[mh] 160
2 multiple sclerosis, relapsing-remitting[mh] 59
3 multiple sclerosis OR "multiple scleroses" 180
4 ("disseminated sclerosis" OR "disseminated scleroses" OR "sclerosis multiplex" OR "insular sclerosis" OR "insular scleroses" OR "encephalomyelitis disseminata" OR "chariot disease") 0
5 (ms OR rms OR rrms) 21
6 #5 OR #4 OR #3 OR #2 OR #1183
7 natalizumab[mh] 6
8 natalizumab* 22
9 (an100226 OR an-100226 OR "an 100226" OR an100226m OR an-100226m OR "an 100226m" OR antegran* OR antegren* OR bg0002 OR bg-0002 OR "bg 0002" OR dst356a1 OR dst-356a1 OR "dst 356a1" OR pb006 OR pb-006 OR "pb 006" OR tysabri*) 18
10 (189261-10-7 OR "189261 10 7" OR 3jb47n2q2p) 0
11 #10 OR #9 OR #8 OR #7 36

12 #11 AND #6 18

Source 6: Conference Proceedings Citation Index – Science (CPCI-S)

Interface / URL: Web of Science
Database coverage dates: 1990 to present
Search date: 17 January 2023
Retrieved records: 70
Search strategy:

Search were performed with "exact search" activated. The final line below was restricted by publication date to those published between "2020-01-01" and "2023-12-31" to reflect the eligibility criteria for conference abstracts.

1 TS="multiple scleros*" 26,830
2 TS=("disseminated scleros*" OR "sclerosis multiplex" OR "insular scleros*" OR "encephalomyelitis disseminata" OR "chariot disease") 8
3 TS=(ms OR rms OR rrms) 79,672
4 #3 OR #2 OR #1 103,401
5 TS=natalizumab* 1,365
6 TS=(an100226* OR an-100226* OR an100226m* OR an-100226m* OR antegran* OR antegren* OR bg0002* OR bg-0002* OR dst356a1* OR dst-356a1* OR pb006* OR pb-006* OR tysabri*) 83
7 TS=(189261-10-7 OR 3jb47n2q2p) 0
8 #5 OR #6 OR #7 1,384
9 #4 AND #8 843
10 #4 AND #8 70

D.1.2 Eligibility criteria

The inclusion and exclusion criteria for the literature review are provided in Table 16.

Table 16: Eligibility criteria for the literature review

	Inclusion criteria	Exclusion criteria
Population	Studies in adults (≥ 18 years) with a confirmed diagnosis of RRMS and meeting criteria consistent with sub-optimally treated HA RRMS: • Unchanged or increased relapse rate compared with the previous year. • Failed to respond to a full and adequate course of disease modifying therapy (DMT). • At least one relapse in the previous year while on therapy.	• Healthy volunteers. • Patients < 18 years of age. • Patients with SPMS, PPMS and PRMS.
Intervention	Natalizumab (Tysabri®).	Other interventions.

Comparators	Any comparator (including placebo or best supportive care) or no comparator.	No excluded comparators.
Outcomes	Efficacy outcomes: • Mortality. • ARR. • Proportion of patients with relapse/relapse free. • Time to first relapse. • Proportion of patients with confirmed disability progression or improvement (3, 6 or 12-month confirmed). • Time to confirmed disability progression or improvement. • Change in disease-specific clinical scores: e.g. Expanded Disability Status Scale (EDSS). • HRQoL: e.g. SF-36, EQ-5D. • MRI-ascertained lesion burden (T2 and Gd-enhanced lesions). Discontinuation outcomes: • Discontinuations due to any cause. • Discontinuation due to treatment failure. • Discontinuations due to AEs. • Discontinuation due to treatment success. • Time to discontinuations. Safety outcomes: • Proportion of patients with any AEs. • Proportion of patients with any SAEs. • Proportion of patients with a specific AE occurring in ≥ 5% of patients in at least one treatment arm.	• Pharmacokinetics studies. • Studies assessing outcomes not relevant to the review.
Study design	• Non-RCTs. • Single arm trials. • Retrospective and observational studies.	• Reviews. • Case reports.
Limits	• No restriction on language. • No restriction on country. • No limit on date for full-text publications.	• Conference abstracts published before 2020. • Letters, preprints, news items, commentaries and editorials.

Abbreviations: AE, adverse event; ARR, annualised relapse rate; DMT, disease-modifying therapy; EDSS; Expanded Disability Status Scale; EQ-5D, EuroQol-5 Dimensions; Gd, gadolinium; HA RRMS; highly active relapsing–remitting multiple sclerosis; HRQoL, health-related quality of life; MRI, magnetic resonance imaging; PPMS, primary progressive multiple sclerosis; PRMS, progressive relapsing multiple sclerosis; RCT, randomised controlled trial; SAE, serious adverse events; SF-36, Short Form-36; SPMS, secondary progressive multiple sclerosis
Source: Chappell et al. (draft manuscript)[44]

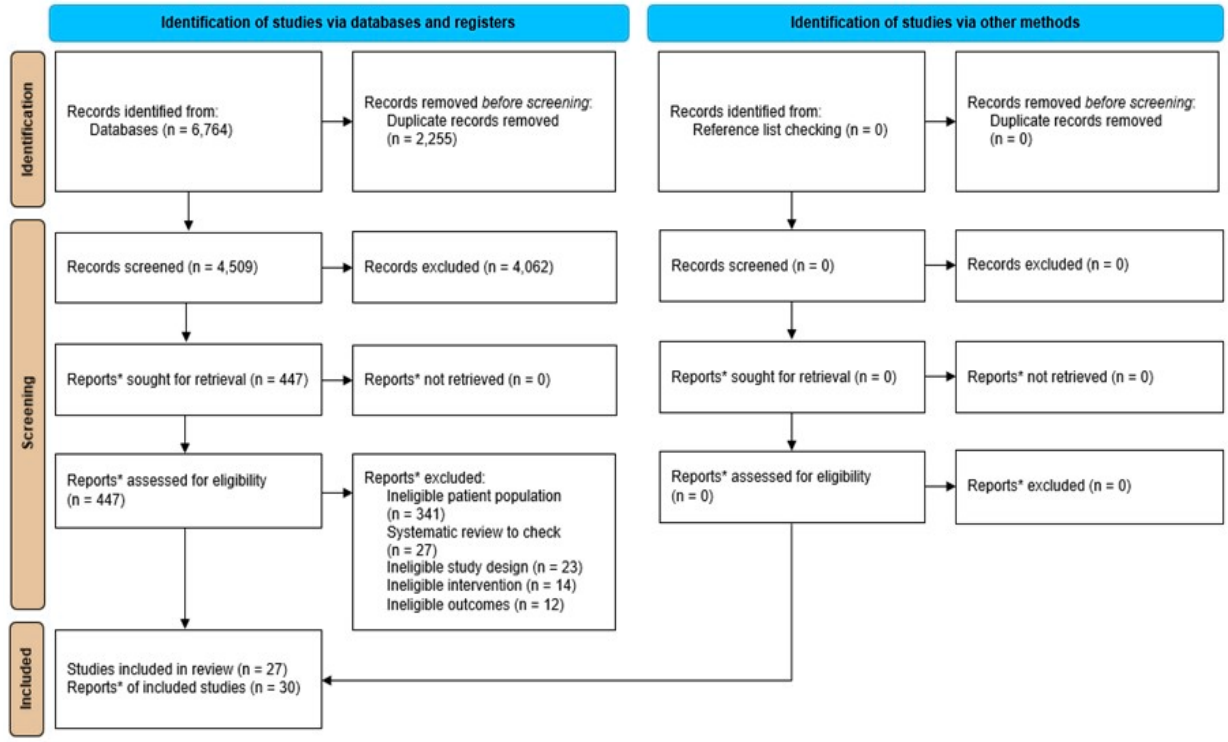
D.1.3 Data extraction

One reviewer assessed the titles, abstracts and full texts for relevance against the eligibility criteria. A second reviewer checked 10% of studies excluded at each stage and all included studies. Data extraction (into a Microsoft Excel template) was conducted by one reviewer, and every data point was checked by a second reviewer.

D.2 Results

The searches identified 4,509 unique records. Following the screening of titles and abstracts, 447 records were assessed at full-text screening. Of these, 417 were excluded and 27 studies (in 30 publications) were included in the review (one non-RCT, 15 cohort studies and 11 case series [in 14 publications]). The PRISMA diagram is provided in Figure 12.

Figure 12: PRISMA diagram depicting the flow of studies



Source: Chappell et al. (draft manuscript)[44]

D.3 Complete reference lists for included studies

The characteristics of the 27 non-RCT studies included in the literature review are provided in Table 17.

Table 17: Included studies in the literature review

Study	Design	Relapse criteria	Intervention/ Comparator	N	Duration of disease (years) Mean (SD)	Previous year relapse rate Mean (SD)	EDSS score mean (SD)/median (range)	Treatment prior to natalizumab-TYS	Duration of natalizumab-TYS treatment
Mazdeh 2018[79]	Non-RCT	≥2 relapses in last year	Natalizumab-TYS	20	9.1 (4.79)	NR	NR	IFN-beta	12 months
			IFN-beta	30	8.77 (2.5)	NR	NR	IFN-beta in prior year al	12 months
Bergvall 2014[80]	Cohort study	≥1 relapse	Natalizumab-TYS	185	NR	1.52 (0.85)	NR	Any DMT: 100% including: GA: 41% IFN: 67%	360 days
			Fingolimod	185	NR	1.56 (0.93)	NR	Any DMT: 100% including: GA: 47% IFN: 57%	360 days
Guerra 2021[81]	Cohort study	≥1 relapse in last year	Natalizumab-TYS	87	10.97 (6.87)	1.17 (0.73)	Median 4.0 (1.5 to 7.5)	IFN-beta or GA	>4 years
			Fingolimod	87	11.08 (7.41)	1.14 (0.82)	Median 3.5 (1.5 to 8.0)	IFN-beta or GA	>4 years
Jamroz-Wisniewska 2021[82]	Cohort study	≥2 relapses in last year	Natalizumab-TYS	101	9.8 (4.7)	2.1 (0.6)	3.2 (1.4)	Overall (not shown by treatment group): IFN-beta: 82%	>1 year
			Fingolimod	180	11.2 (5.7)	2.0 (0.7)	3.3 (1.3)		>1 year

								With GA: 16% Other drugs: 2%	
Kalincik 2015[83]	Cohort study	≥1 relapse in last 6 months	Natalizumab-TYS	311	9.4 (6.2)	1.53 (1.04)	3.4 (1.5)	IFN-beta or GA	Mean (SD): 12 (7) months
			Fingolimod	121	9.5 (8.0)	1.29 (0.86)	3.1 (1.7)	IFN-beta or GA	Mean (SD): 12 (7) months
Kapica-Topczewska[84]	Cohort study	≥2 relapses	Natalizumab-TYS	358	NR	NR	Median 3.5	NR	Up to 4 years
			Fingolimod	682	NR		Median 3.0	NR	Up to 4 years
Lanzillo 2013[85]	Cohort study	≥1 relapse	Natalizumab-TYS	50	NR	1.66 (1.21)	Median 4 (1.5 to 7)	Rebif 22: 10% Rebif 44: 38% Avonex: 18% Betaferon 22% Copaxone 12%	12 months in 72% patients and 24 months in 28% patients
			Prior DMTs	50	NR	1.26 (0.88)	Median 2.5 (0 to 5.5)	NA	Mean (SD): 4.4 (2.8) years
Lorscheider 2018[86]	Cohort study	≥1 relapse	Natalizumab-TYS	179	7.4 (6.6)	2.8 (2.0)	Median 3.0 (IQR: 2.0 to 3.5)	IFN-beta 1a (intramuscular): 26% IFN-beta 1a (subcutaneous): 33% IFN-beta 1b (subcutaneous): 22% GA: 19%	Up to 3 years

			Fingolimod	179	8.0 (6.3)	2.7 (3.1)	Median 2.5 (IQR: 2.0 to 3.5)	IFN-beta 1a (intramuscular): 25% IFN-beta 1a (subcutaneous): 38% IFN-beta 1b (subcutaneous): 18% GA: 20%	Up to 3 years
Meca-Lallana 2020[87]	Cohort study	NR	Natalizumab-TYS	130	7.01 (5.17)	1.56 (0.77)	3.08 (1.56)	NR	Up to 48 months
			Fingolimod	184	7.06 (5.56)	1.64 (0.91)	2.65 (1.42)	NR	Up to 48 months
Prosperini 2012[88]	Cohort study	≥2 relapses or ≥1 relapse with sustained worsening disability	Natalizumab-TYS (escalation group)	106	8.7 (5.3)	1.80 (0.71)	2.8 (1.1)	Low-dose IFN-beta: 15.1% High-dose IFN-beta: 78.3% GA: 6.6%	24 months
			Switch among immunomodulators (switching group)	161	8.9 (6.2)	1.61 (0.65)	2.5 (1.1)	Prior to switching immunomodulators: Low-dose IFN-beta: 73.9% High-dose IFN-beta: 22.4% GA: 3.7%	24 months
Prosperini 2017[89]	Cohort study	≥2 relapses or ≥1 relapse with a EDSS score of ≥2 in the past year	Natalizumab-TYS	110	8.5 (5.8)	1.4 (0.5)	2.7 (1.1)	NR	24 months
			Fingolimod	110	7.8 (5.8)	1.4 (0.6)	2.6 (1.1)	NR	24 months
			Alternative self-injectable DMD (from IFN-beta or GA, or vice versa)	110	8.5 (6.3)	1.4 (0.5)	2.7 (1.3)	NR	24 months
Puz 2016[90]	Cohort study	≥2 relapses	Natalizumab-TYS	14	NR	Across treatment groups	Median 4.0 (range 1.0 to 6.0)	Across treatment arms: IFN-beta-1b: 34.1%	Across both arms, mean

			Fingolimod	30	NR	2.13 (0.87)	Median 4.0 (range 1.0 to 6.0)	IFN-beta-1a (subcutaneous): 13.6% IFN-beta-1a (intramuscular): 18.2% GA: 34.1%	(SD): 16.3 (6.36) months
Sempere 2013[91]	Cohort study	NR	Natalizumab-TYS	9	10.4 (NR)	1.67 (0.71)	2.67 (1.56)	NR	12 to 15 months
			Fingolimod	8	11.1 (NR)	0.13 (0.35)	2.88 (1.87)	Natalizumab-TYS: 100%	4 to 12 months
Spelman 2015[92]	Cohort study	≥1 relapse in the past 12 months	Natalizumab-TYS	869	Median 6.8 (IQR: 3.4 to 12.0)	1.6 (0.7)	Median: 3 (IQR: 2 to 4)	Betaferon, Betaseron, Rebif, Avonex, Copaxone, or Extavia: 100%	Mean (SD): 1.95 (1.23) years
			IFN-beta/GA (BRACE)	869	Median: 6.2 (IQR: 3.0 to 11.6)	1.6 (0.9)	Median: 3 (IQR: 2 to 4)	Betaferon, Betaseron, Rebif, Avonex, Copaxone, or Extavia: 100%	Mean (SD): 2.24 (2.47) years
Spelman 2022[93]	Cohort study	≥1 relapse in the past year before switching treatment	Natalizumab-TYS	897	Median 7.7 (IQR 3.6 to 12.7)	1.5 (0.7)	Median: 2.5 (IQR: 1.5 to 4.0)	IFN-based therapies, GA, dimethyl fumarate, or teriflunomide Betaferon: 10.5% Rebif: 31.9% Avonex: 20% Copaxone: 25.1% Extavia: 10.5% Aubagio: 0.3% Tefidera: 1.8%	Mean (SD): 2.56 (1.71) years
			Fingolimod	897	Median 7.8 (IQR: 3.8 to 13.9)	1.5 (0.7)	Median: 2.5 (IQR: 1.5 to 4.0)	IFN-based therapies, GA, dimethyl fumarate, or teriflunomide Betaferon: 9.8%	Mean (SD): 2.05 (1.27) years

								Rebif: 34.6% Avonex: 18.1% Copaxone: 24.4% Extavia: 9.8% Aubagio: 1.1% Tefidera: 2.2%	
			Switch to another first-line therapy (IFN-based therapies, GA, dimethyl fumarate, and teriflunomide)	897	Median 7.7 (IQR: 3.5 to 12.6)	1.5 (0.7)	Median 2.5 (IQR: 1.5 to 4.0)	IFN-based therapies, GA, dimethyl fumarate, or teriflunomide Betaferon: 8.5% Rebif: 35.9% Avonex: 29% Copaxone: 15.8% Extavia: 8.5% Aubagio: 1% Tefidera: 1.2%	Mean (SD): 1.99 (1.52) years
Wiebenga 2016[94]	Cohort study	≥1 relapse	Natalizumab-TYS	22	8.3 (6.2)	NR	Median 3.0 (range 1.5 to 6.5)	IFN-beta or GA	12 months
			IFN-beta or GA	17	9.1 (5.2)	NR	Median: 2.5 (range1.0 to 6.5)	IFN-beta or GA	12 months
Belachew 2011[95]	Case series	≥1 relapse in the past year	Natalizumab-TYS	45	Median 7.0 (range 1 to 24)	1.87 (0.73)	3.5 (1.3)	GA in the previous year: 27% IFN-beta in the previous year: 73%	44 weeks
Butzkueven 2020[59]	Case series	NR	Natalizumab-TYS	2,897	Median 7.8 (range 0 to 48)	2.0 (1.0)	3.5 (1.6)	NR	Median 3.3 (range 0 to 11.6) years
Calabrese 2017[96]	Case series	NR	Natalizumab-TYS	39	NR	NR	Median 2.0 (range 1.0 to 3.5)	Treatment preceding natalizumab-TYS: IFN-beta1a: 46.2% IFN-beta1b: 12.8% GA: 28.2% Fingolimod: 15.4%	Mean (SD): 28.3 (5.3) months

								Immunosuppressive therapy (cyclophosphamide): 17.9%	
Fernández-Megía 2011[97]	Case series	NR	Natalizumab-TYS	30	Median 9 (range 14 to 41)	Median 2 (range 1 to >3)	Median 3 to 3.5 (range 1 to >5)	NR	NR
Fragoso 2013[98]	Case series	NR	Natalizumab-TYS	103	NR	NR	NR	IFN-beta or GA: 100%	NR
Magraner 2012[99]	Case series	≥2 relapses in the past year or ≥1 relapse with MRI scan identifying lesions	Natalizumab-TYS	18	7.2 (5.7)	2.0 (1.1)	3.1 (0.9)	IFN-beta (Rebif, Avonex or Betaferon): 50% Rebif + Azathioprine: 5.6% Rebif + methylprednisolone: 5.6% Betaferon + methylprednisolone: 5.6% GA (Copaxone): 16.7% Mitoxantrone: 1 5.6% Fingolimod: 0% Daclizumab: 11.1%	18 months
Oliveira 2015[100]	Case series	≥1 relapse	Natalizumab-TYS	75	11.84 (7.39)	2.45 (1.86)	4.15 (1.72)	IFN and GA: 66.7% IFN or GA: 30.7% Neither: 2.7%	12 months
Oturai 2009[101]	Case series	≥2 relapses or sustained increase of 2 EDSS points on DMT	Natalizumab-TYS	175	Median 8 (range 0 to 36)	2.71 (95% CI: 2.46 to 2.97)	Median 4.0 (range 0 to 7.5)	DMT (no further information)	Median (range) 10.0 (3.0–21.5) months

Popova 2014[102]	Case series	≥1 relapse	Natalizumab-TYS	69	NR	1.81 (NR)	3.73 (1.12)	Colpaxone: 24.2% Betaferon: 20.0% Refib: 12.6% Refib-22: 3.1% Ronbetal: 11.6% Extavia: 9.5% Avonex: 6.3% Genfaxon: 6.3% No DMTs: 6.3%	12 months
Putzki 2009[103]	Case series	≥1 relapse	Natalizumab-TYS	31	7.83 (4.58)	2.1 (1.4)	3.4 (1.1)	IFN-beta: 74.2% GA: 25.8%	12 months
Rinaldi 2011[104]	Case series	NR	Natalizumab-TYS	35	9.1 (6.8)	2.2 (1.0)	3.2 (1.1)	IFN-beta and/or GA: 100%	12 months

Abbreviations: DMT, disease-modifying therapy, EDSS, Expanded Disability Status Scale; GA, glatiramer acetate; IFN, interferon; MRI, magnetic resonance imaging; NA, not applicable; Natalizumab-TYS, natalizumab (Tysabri®); NR, not reported; SD, standard deviation
Source: Chappell et al. (draft manuscript)[44]

Appendix E: Subgroup analysis

Not applicable.

Appendix F : Adverse reactions

Not applicable.

Appendix G: Published cost-effectiveness studies

Not applicable.

Appendix H: Health-related quality-of-life studies

Not applicable.

Appendix I: Costs and healthcare resource use identification, measurement and valuation

Not applicable.

Appendix J: Clinical outcomes and disaggregated results from the model

Not applicable.

Appendix K: Price details of treatments included in the submission

Not applicable.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple sclerosis (relapsing, remitting, highly active) – natalizumab and Tyruko (biosimilar natalizumab) (after disease modifying therapy) [ID6369]

Sandoz Ltd
Biosimilar natalizumab (Tyruko)
Company submission

Sandoz confirm that all information in the submission summary is an accurate summary or replication of evidence in the main submission and accompanying appendices and that wherever possible a cross reference to the original source is provided.

August 2024

File name	Version	Contains confidential information	Date
Natalizumab ID6369 [noCON] Sandoz evidence submission - version 1.1 _REDACTED FINAL	**Version 1.0**	**Yes**	**16/08/2024**

Contents

Tables and figures

Abbreviations

Abbreviation	Definition
ABN	Association of British Neurologists
BMI	Body mass index
BNF	British National Formulary
DMT	Disease modifying therapy
CI	Credible interval
ECTRIMS	European Committee for Treatment and Research in Multiple Sclerosis
EDSS	Expanded Disability Status Scale
EID	Extended interval dosing
EMA	European Medicines Agency
FDA	Food and Drug Administration
HA RRMS	Highly active relapsing remitting multiple sclerosis
IV	Intravenous
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
PAS	Patient access scheme
PML	Progressive multifocal leukoencephalopathy
RRMS	Relapsing remitting multiple sclerosis
SC	Subcutaneous
SmPC	Summary of Product Characteristics
TA	Technology appraisal
UK	United Kingdom

Executive Summary

- There is clear patient and clinical value in expanding the National Institute for Health and Care Excellence (NICE) recommendation for natalizumab to include treatment of the 'highly active' relapsing remitting multiple sclerosis (HA RRMS) population and hence allow use of natalizumab in its full licensed population.
- The use of natalizumab across its full licensed indications is supported by clinical guideline recommendations from the Association of British Neurologists (ABN) and European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS), as well as real-world evidence.[1, 2]
- As a 'high-efficacy' disease-modifying therapy (DMT), the most relevant comparators to natalizumab represent the other high efficacy DMTs that are used in United Kingdom (UK) clinical practice: ocrelizumab and ofatumumab. A published systematic literature review and network meta-analysis (NMA) supports comparable efficacy of natalizumab and these comparators.[3] Although this NMA was conducted in the whole RRMS population and not restricted to HA RRMS patients only, there is precedent from the NICE appraisal of ofatumumab for considering whole trial evidence generalisable to HA RRMS when assessing comparative effectiveness.[4]
- Biosimilar natalizumab (Tyruko) has demonstrated bioequivalence with the originator natalizumab (Tysabri).[5] Expanding the NICE recommendation for natalizumab to encompass its full licensed population will not only provide an important additional clinical option for healthcare professionals and patients, but it will also enable use of a DMT for which there is a biosimilar option available, supporting the National Health Service's (NHS) medicines optimisation goals and helping to drive cost savings.[6-8] Prices in markets where biologic and biosimilars compete – as here – are dynamic, mediated through competitive tenders, and tend to fall over time for the biosimilar and originator. This contrasts with new, on-patent medicines for which pricing is usually stable for the period of exclusivity.[1] Biosimilar competition is important for creating the environment for these beneficial pricing dynamics.
- A simple cost comparison based on drug acquisition and administration costs finds the modelled treatments (biosimilar natalizumab intravenous [IV; Tyruko], originator natalizumab IV [Tysabri], originator natalizumab subcutaneous [SC; Tysabri], ofatumumab and ocrelizumab) to be associated with similar costs over a 3 year time horizon when considered at list price. The potential for extended interval dosing (EID) with IV natalizumab reduces the costs associated with originator natalizumab (Tysabri) and biosimilar natalizumab (Tyruko).

[1] Unless price changes are triggered by other factors, for example by entry of the medicine into a new indication at which a different price is required for cost-effectiveness

Company Submission

A.1 Health condition

Multiple sclerosis (MS) is a complex and fundamentally unpredictable condition. RRMS is characterised by defined episodes of new or increasing neurologic symptoms (relapses), followed by periods of partial or complete recovery (remission), where symptoms may either disappear entirely or some symptoms persist long term.[9] The symptoms experienced by individuals with RRMS vary from patient to patient, and symptoms can affect any part of the body. Common symptoms may include, for example: difficulty walking, numbness or tingling in the face, arms or legs, problems with vision, fatigue, vertigo and dizziness, cognitive and emotional changes, depression, pain and itching, weakness, bladder and bowel dysfunction, sexual dysfunction, and spasticity, including muscle stiffness and involuntary contractions.[10] MS is a progressive disease, meaning that over time the disease worsens and the flare-ups can become more frequent and more debilitating, ultimately leading to a higher burden of disability. In more progressed stages of the disease this can pose a considerable health burden on the patient and also lead to the need for significant support from carers, such as family members.

Given the complex nature of the condition, the choice of treatment is highly dependent on each patient and their individual circumstances. Sandoz therefore welcomes this appraisal to consider the extension of the NICE recommendation for natalizumab to include the HA RRMS population in order to make this treatment option available to patients.

Sandoz understands that any NICE recommendation would need to be within the licensed indication of natalizumab. Hence, a focus of this appraisal on the HA RRMS subgroup is appropriate as it is consistent with the part of natalizumab's licence wording that is not currently recommended by NICE. However, it is important that the assessment takes into account the context surrounding the definition of "highly active" in RRMS as this has important implications for the evidence that should be used to inform the appraisal.

In clinical practice, different forms of MS are often not clearly defined and are instead considered to be part of a wider disease spectrum. As such, 'highly active' disease is not constrained by a strict definition in clinical practice. This can be seen by the fact that varying definitions of the 'highly active' subgroup have been used across the marketing authorisation wording and NICE appraisals of DMTs. For example, previous appraisals in this indication have utilised varied criteria relating to previous relapses and lesions on magnetic resonance imaging (MRI). In clinical practice, Sandoz understands the preference among clinicians is to maintain a broad definition of highly active disease, enabling clinician discretion to determine whether a patient classifies as 'highly active' or 'active'. This is reflected in the discussion at Committee meetings of prior NICE appraisals in MS. This is important to note because it demonstrates that the highly active subgroup of RRMS is a variably defined subgroup based on historical licensing considerations specific to each DMT. These considerations aimed to consider unmet need and appropriate populations for balancing benefit and risk of the specific new DMT being licensed, and also in relation to available clinical trial data supporting the regulatory application.[11] HA RRMS does not represent a clearly defined

patient subpopulation in practice and does not represent a clinical subgroup for which there is clear evidence for differential treatment effect compared to the full RRMS population.

It is important that during this multiple technology appraisal the HA RRMS subgroup is viewed through this lens as this has important implications for how available evidence is considered. Reflecting the origins and nature of the HA RRMS subgroup, many of the DMTs that are licensed and reimbursed in RRMS do not possess robust evidence in the specific subgroup of patients with HA RRMS. This is highlighted by the NICE appraisal of ofatumumab for RRMS (TA699), in which the Evidence Review Group highlighted a paucity of comparative effectiveness data for the highly active subgroup and therefore agreed with the manufacturer's approach to utilise the full trial data to inform the NMA used to assess relative treatment effects for this subgroup.[4]

In this context, Sandoz strongly advocates that the clinical case for expanding natalizumab use into the full licensed population should *not* be based solely on consideration of subgroup data specific to the HA RRMS population. A lack of robust subgroup-specific data for the highly active subgroup has not precluded a positive recommendation for other DMTs in the whole RRMS population (and therefore by definition also the highly active subgroup within that), with precedent for assuming that whole trial evidence provides an estimation of treatment effect in the highly active subgroup. It is because of the licence wording that the decision problem for this appraisal needs to focus on the HA RRMS subgroup as defined in the natalizumab licence. It is important that the evidence assessment takes into account the above context, otherwise there is a risk that natalizumab is held to a different standard of evidence demonstration than has been applied for other DMTs. Furthermore, an assessment of comparative effectiveness based on highly active subgroup-specific data will be naturally limited by data availability to inform robust comparison.

A.2 Clinical pathway of care

The role of DMTs, including natalizumab

DMTs are a vital part of the MS treatment paradigm, representing the mainstay of treatment for patients with RRMS. Whilst there are a number of DMTs licensed and reimbursed for the treatment of HA RRMS, these have varying levels of efficacy and side-effects and consequently different benefit-risk profiles. As such, the choice of treatment is highly dependent on each patient and their individual circumstances, and different DMTs would be best suited to different contexts. Availability of a range of DMTs is therefore important in providing clinicians and their patients with the ability to tailor treatment choice, whilst taking into account patient characteristics and the balance of benefit and risk that is suitable for the patient.

Natalizumab is a monoclonal antibody DMT classed as a drug of 'high efficacy' as per ABN guidelines, corresponding to an average relapse reduction substantially more than 50%.[1] Natalizumab would therefore be used in patients for whom a high-efficacy biologic treatment is considered the most appropriate treatment approach on the balance of benefit and risk in the context of the patient need. This is reflected in ABN guidelines, which state that "alemtuzumab and natalizumab are appropriate where individuals and their multiple sclerosis

specialist neurologists are most concerned to achieve high efficacy, despite the more complex safety profile compared to Category 1 drugs".[1]

Currently, natalizumab is not available as an option for patients with HA RRMS in England due to the restricted NICE guidance from TA127. This leaves this patient group with a more restricted set of treatment options, and particularly with regard to options for treatment with a high efficacy. This represents an important unmet need; a consensus statement published in 2022 highlights the clinical importance to patients of timely access to high-efficacy DMTs.[12, 13] Furthermore, the reason that the HA RRMS subgroup was explicitly defined in the natalizumab marketing authorisation was because this was identified as a group of particularly high unmet medical need and for which natalizumab would represent a viable treatment option taking into account its benefit-risk profile.[11]

In contrast to this NICE recommendation, natalizumab is recommended by the ABN for treatment in its full licensed population, including both HA RRMS and rapidly evolving severe RRMS. ABN categorise DMTs based on efficacy, with Category 1 defined as moderate efficacy and Category 2 drugs, including natalizumab, defined as high efficacy. Category 1 treatments are recommended for the first-line treatment of RRMS, and Category 2 treatments are recommended in patients with 'more active' RRMS, in which the frequency of MRI activity and/or clinical relapse is still high after either Category 1 or no treatment.[1] The ECTRIMS guidelines also reflect this, recommending more efficacious treatments such as natalizumab in cases where patients previously treated with moderate DMTs continue to show further disease activity.[2] Therefore, leading MS guideline organisations at the UK and European level both recognise the clinical value of natalizumab in its full licensed population, including HA RRMS.

Since the original NICE appraisal of natalizumab, there have been real-world studies demonstrating the efficacy of natalizumab, including in the HA RRMS group. Studies also support that early (within 2 years from disease onset) use of high efficacy DMTs, including natalizumab, results in improved long-term outcomes for people with MS. This further supports the need to make a high-efficacy DMT, such as natalizumab, available so that patients can realise the benefits that early treatment with higher efficacy biologics can provide. In addition, Sandoz is able to point to a number of patient case studies that are illustrative of the types of patients that are currently denied access to natalizumab, either due to the NHS England algorithm or because of variations in interpretation of the criteria, but whom we feel have evidence-based reasons to benefit from this treatment. Sandoz has previously articulated these evidence sources and case studies in a proposal document to NHS England, which is attached as a supplement to this submission.[14]

In summary, there is a clear clinical rationale for natalizumab to be available to patients with HA RRMS and this would be important in addressing a need for more high-efficacy DMT options for these patients. The clinical value that natalizumab can provide for patients with HA RRMS in the UK was highlighted during the COVID-19 pandemic. During this period, NHS England took the decision to expand use of natalizumab to include all patients within its licence.[15] This was likely due to the favourable profile of natalizumab in comparison to anti-CD20 antibodies, including other high-efficacy drugs ofatumumab and ocrelizumab, with regard to immunosuppression. As a result of this decision, a 46.9% increase in initiation of natalizumab was seen in 2020 relative to 2019, supporting a clear clinical role for

natalizumab within its broader licensed population i.e. beyond the original, optimised NICE guidance.[16]

Relevant comparators to natalizumab

Alternative licensed high-efficacy biologic treatments other than natalizumab are ocrelizumab, ofatumumab and alemtuzumab. Ocrelizumab and ofatumumab were licensed after the 2015 ABN guidelines were published and therefore are not included in the 'high efficacy' classification in these guidelines. However, these two therapies are generally considered to be 'high efficacy' alongside natalizumab and alemtuzumab. This is consistent with the MS Decision Aid published by the MS Trust, which categorises DMTs into 'moderately effective', 'more effective' and 'highly effective' based on broad categories recommended in guidelines from the ABN: natalizumab, ocrelizumab and ofatumumab (as well as alemtuzumab) are the only DMTs categorised as 'highly effective'.

Whilst alemtuzumab is classed as a high-efficacy/highly effective DMT alongside natalizumab, alemtuzumab is associated with a specific and complex safety profile that has restricted its use in UK clinical practice, and Sandoz understands that alemtuzumab has limited usage in practice as a treatment option among patients with 'highly active' RRMS.[17, 18]

As such, ofatumumab and ocrelizumab represent the most relevant comparators to natalizumab for patients with highly active disease after at least one DMT, as these are the other treatment options that are available for contexts where the patient requires a high efficacy DMT.

Biosimilar natalizumab – the role of biosimilars in the NHS

Biological medicines are currently the largest cost and cost growth areas in the NHS medicines budget;[8] as such, "using best value biologic medicines in line with NHS England commissioning recommendations" is one of NHS England's sixteen national medicines optimisation opportunities for the NHS in 2023/2024.[6] Biosimilar natalizumab offers an opportunity to support the potential identified by the NHS to deliver savings of up to £300m each year through use of biosimilars, enabling more patients to have access to other life-saving and life-enhancing treatments.[8] Reports from the NHS Long-Term Plan have demonstrated the value that driving uptake of biosimilars can provide in terms of cost-savings and opportunities for reinvestment.[7] A further report on the impact of biosimilar competition in Europe in 2023 notes that biosimilar uptake is a key contributor to savings and provides uptake metrics (Exhibit 8 in the report) that indicate high uptake of a number of biosimilars in the UK, supporting the value that biosimilars in general are offering to the UK healthcare system.[19]

Therefore, expanding the NICE recommendation for natalizumab to encompass its full licensed population will not only provide an important additional clinical option for healthcare professionals and patients, as outlined above, but it will also enable use of a DMT for which there is a biosimilar option available, supporting the NHS' medicines optimisation goals and helping to drive cost savings.

A.3 Equality considerations

Not applicable.

A.4 The technology

Table 1: Technology being evaluated

UK approved name and brand name	Biosimilar natalizumab (Tyruko)
Mechanism of action	Natalizumab is a humanised monoclonal antibody that binds to the α4-subunit of α4β1 (also known as very late antigen-4 or VLA-4) and α4β7 integrins, which are adhesion molecules expressed on the surface of all leucocytes except neutrophils. Binding to integrins inhibits the α4-mediated adhesion of leukocytes to their receptor(s). Disruption of these molecular interactions prevents transmigration of leukocytes across the endothelium into inflamed parenchymal tissue. This blocking of leukocyte migration from the blood vessels to the central nervous system prevents them from exerting pro-inflammatory responses thereby reducing inflammation.
Marketing authorisation/CE mark status	Tyruko holds a marketing authorisation with the Medicines and Healthcare Products Regulatory Agency (MHRA) and the European Medicines Agency (EMA)
Indications and any restriction(s) as described in the summary of product characteristics	Tyruko is indicated in the same populations as the originator natalizumab (Tysabri). Tyruko is indicated as a single disease modifying therapy (DMT) in adults with highly active relapsing-remitting multiple sclerosis (HA RRMS) for the following patient groups: • Patients with highly active disease despite a full and adequate course of treatment with at least one DMT, or • Patients with rapidly evolving severe RRMS defined by 2 or more disabling relapses in one year, and with 1 or more Gadolinium enhancing lesions on brain Magnetic Resonance Imaging (MRI) or a significant increase in T2 lesion load as compared to a previous recent MRI. The population relevant to this NICE appraisal is the former, relating to patients with highly active disease. Natalizumab (and therefore biosimilar natalizumab) is already recommended by NICE in the population of patients with rapidly evolving severe RRMS.

Method of administration and dosage	Biosimilar natalizumab (Tyruko) is administered by intravenous infusion at a dose of 300 mg once every 4 weeks.
Additional tests or investigations	No additional tests or investigations are required to determine that a patient meets the criteria for highly active disease as per the marketing authorisation. As noted in our submission, in clinical practice different forms of MS are often not clearly defined and are instead considered to be part of a wider disease spectrum. As such, 'highly active' disease is not constrained by a strict definition in clinical practice. However, clinicians make the judgement as to when natalizumab can be used within the terms of its marketing authorisation (i.e. when natalizumab is appropriate for the level of disease activity and the patient has previously received a full and adequate course of a prior DMT) – there is no specific diagnostic test or investigation required to determine eligibility for highly active disease as per the marketing authorisation.
List price and average cost of a course of treatment	The list price of biosimilar natalizumab (Tyruko) is £1,017.00 per 300 mg vial.
Patient access scheme (if applicable)	Biosimilar natalizumab (Tyruko) has a confidential commercial price as a result of a competitive tendering process. The current confidential price of biosimilar natalizumab (Tyruko) is £[redacted] per 300 mg vial. This corresponds to a [redacted] discount on the current list price of Tysabri. It should be noted that in markets where biosimilars and originator biologics compete – as is the case here – prices are dynamic and mediated through competitive tenders, and tend to fall over time. For example, Sandoz observes that the prevailing prices for adalimumab, etanercept and infliximab are lower in 2024 than they were when TA715 was published in 2021.[20] The adapted MTA methodology applied to this appraisal and TA715 uses framework tender prices, which are inherently dynamic. Although Sandoz can neither commit to future discounts for biosimilar natalizumab (Tyruko) nor predict the pricing strategy of originator natalizumab (Tysabri), past experience demonstrates that there is potential for higher discounts over a much shorter time frame than the price reductions that tend to be seen for the new medicines that NICE typically assesses

Intravenously-administered versus subcutaneously-administered formulations of natalizumab

As noted in the final scope for this appraisal, originator natalizumab (Tysabri®) has a marketing authorisation for IV and SC administration, whereas biosimilar natalizumab (Tyruko®) has a licence for IV administration only.

In UK clinical practice, patients and clinicians value choice in route of natalizumab administration, with different advantages associated with each formulation. Sandoz emphasises that, while patients may be switched from one formulation onto the other after careful consideration based on a clear rationale, subcutaneously administered and intravenously administered natalizumab should not be considered as interchangeable and it is important to note the factors that support the benefit of availability of the IV formulation of natalizumab for patients with HA RRMS.

- The volume and quality of evidence for the efficacy of the IV formulation is significantly greater than that for the SC formulation. The SC formulation of natalizumab was granted marketing authorisation by the European Medicines Agency (EMA) in April 2021 on the basis of two studies (DELIVER and REFINE).[21-23] DELIVER was a study in patients who were naïve to prior natalizumab IV but had a primary objective to compare pharmacokinetics and pharmacodynamics and was not powered to detect changes in efficacy outcomes across groups.[22] For REFINE, the study included patients who had been previously treated with natalizumab IV for at least 12 months (i.e. does not provide evidence for patients who initiate natalizumab SC as their first experience of natalizumab) and the EMA noted that the exploratory nature of the study meant that no formal efficacy comparisons were made.[21, 23] Therefore, to date, the vast majority of high-quality evidence for the efficacy and safety of natalizumab continues to be for the IV formulation.[24-26] Published and ongoing studies for SC natalizumab are frequently limited by their small sample sizes among natalizumab SC arms and focus on pharmacokinetic and pharmacodynamic primary outcomes.[27-30] Furthermore, it should be noted that in the United States the Food and Drug Administration (FDA) were unable to approve the filing for the SC formulation of originator natalizumab (Tysabri).[31]
- As noted in the EMA's assessment report for the SC formulation of natalizumab, there is evidence that mean natalizumab trough levels are "slightly, but consistently reduced" with the SC administration compared with IV administration.[32] Findings from the NEXT trial demonstrate that natalizumab trough drug levels are on average 55% lower for SC administration than IV administration.[33] In the study, only 15 participants were switched to SC administration, and of these three required a shorter treatment interval compared to their previous IV regimen, as trough levels on SC fell below 2µg/mL. Therefore, it was indicated that patients with low trough levels of natalizumab during IV dosing, those on extended intervals or those with high body mass index (BMI) may experience subtherapeutic natalizumab concentrations when switched to SC, which has the potential to lead to rebound disease activity.[33] A study published in 2024 comparing single serum trough concentrations between four-weekly SC and IV administration in matched cohorts also found lower trough concentrations with SC (n=25) compared with IV administration (n=25), although concentrations remained largely within the therapeutic range.[34] In an exploratory analysis in a group of 11 patients receiving six-weekly EID with natalizumab

SC, the median trough concentration was even lower, potentially limiting EID as an option with SC natalizumab.[34] As for the REFINE study, it should be noted that the evidence provided by these two studies is only in patients who have previously received natalizumab infusions and not in patients newly initiating on natalizumab SC.

- A key differentiation of IV natalizumab compared to SC natalizumab is the ability to have EID with IV natalizumab. EID lowers drug exposure as the dosing interval is extended to an average of six weeks rather than four weeks; this may help to mitigate the risk of natalizumab-associated adverse events. For example, the EMA marketing authorisation for Tyruko notes that in anti-JCV antibody positive patients (the presence of which represents a risk factor for progressive multifocal leukoencephalopathy [PML]), EID is suggested to be associated with a lower risk of PML compared to the standard four-weekly dosing. The NOVA study provided a prospective, randomised controlled study of patients who switched to IV dosing every six weeks after at least one year of IV treatment every four weeks compared to those who remained on IV treatment every four weeks, and found similar results in terms of clinical efficacy on a number of outcomes related to development of new lesions, annualized relapse rate and EDSS worsening.[5] A growing further body of evidence demonstrates that patients with RRMS can be switched from treatment with IV natalizumab every four weeks to every six weeks, without any meaningful efficacy loss.[35-38] In contrast, the Summary of Product Characteristics (SmPC) for natalizumab SC states that "no clinical data are available on either the safety or efficacy of this extended interval dosing with the subcutaneous route of administration".[21] Indeed, the considerations regarding trough levels with the SC formulation may mean that EID with SC natalizumab would be less feasible due to the risk of reaching subtherapeutic natalizumab concentrations between doses (as per the earlier discussion). In summary, the potential for EID with SC natalizumab remains to be supported to the degree that has been done for IV natalizumab.
- Anecdotally, Sandoz understands that, for some patients, the community aspect of receiving treatment via IV administration, involving time spent in hospital alongside others facing similar challenges, presents an added advantage.

A.5 Decision problem and NICE reference case

The submission focuses on part of the technology's marketing authorisation relating to patients with HA RRMS that meets the criterion of "highly active disease despite a full and adequate course of treatment with at least one disease modifying therapy (DMT)". The focus of the submission is narrower than the marketing authorisation because this represents the part of the marketing authorisation in which NICE does not currently already recommend natalizumab.

The company submission differs from the final NICE scope and the NICE reference case in the areas detailed in Table 2 below.

Table 2: The decision problem

	Final scope issued by NICE/reference case	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with highly active relapsing remitting multiple sclerosis despite a full and adequate course of treatment with at least one disease modifying therapy	Adults with highly active relapsing remitting multiple sclerosis despite a full and adequate course of treatment with at least one disease modifying therapy	N/A
Intervention	• Natalizumab (Tysabri) • Natalizumab biosimilar (Tyruko)	Biosimilar natalizumab (Tyruko)	Sandoz is the manufacturer of biosimilar natalizumab (Tyruko) so this is the intervention of focus for the Sandoz company submission.

Comparator(s)	Standard care without natalizumab or natalizumab biosimilar, including but not limited to:
	• For people with disease activity after 1 disease modifying therapy (DMT):
	  ○ glatiramer acetate
	  ○ interferon beta 1a
	  ○ interferon beta 1b
	  ○ alemtuzumab
	  ○ cladribine tablets
	  ○ fingolimod
		• Originator natalizumab (Tysabri)
		• Ofatumumab
		• Ocrelizumab
			Please see preceding discussion in Section A.2 . The comparators included in this submission are the originator version of natalizumab (Tysabri) as well as the other 'high efficacy' biologics that are used in UK clinical practice as these represent the most relevant treatments that might be considered for treating a patient alternatively to biosimilar natalizumab (Tyruko).

	○ ocrelizumab (if alemtuzumab contraindicated or otherwise unsuitable) ○ ofatumumab ○ ponesimod ○ autologous haematopoietic stem cell transplantation		
Outcomes	The outcome measures to be considered include: • relapse rate • severity of relapse • disability (for example, expanded disability status scale [EDSS]) • disease progression • symptoms of multiple sclerosis (such as fatigue, cognition, and visual disturbance) • freedom of disease activity (for example lesions on MRI scans) • mortality • adverse effects of treatment • health-related quality of life	In contrast to new medicines, where extensive clinical data is essential for approval, biosimilars are developed and approved based on the principle of totality of evidence. This principle is based on analytical and functional comparison of the reference biologic and a biosimilar and the similarity is then verified in a smaller clinical study. Biosimilar natalizumab (Tyruko) has demonstrated equivalence to the originator natalizumab (Tysabri), leading to granting of the marketing authorisation. As such, clinical outcomes for biosimilar natalizumab are not presented in this submission – the clinical outcomes can be assumed	See explanation in the preceding column.

		equivalent to those of originator natalizumab (Tysabri). A short summary of the ANTELOPE study that demonstrated that biosimilar natalizumab matched originator natalizumab in terms of efficacy, safety and immunogenicity is provided in Section A.6 and A.7 .	
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year.	Cost comparison analysis based on drug acquisition and administration costs	The economic analysis presented in this submission is a simplified analysis consisting of a cost comparison. This is on the basis of equivalent efficacy between biosimilar natalizumab (Tyruko) and originator natalizumab (Tysabri) and an assumption of comparable efficacy of natalizumab with ofatumumab and ocrelizumab. Sandoz considers this represents a proportionate approach to the economic analysis given the scope of the appraisal and Sandoz's position as a biosimilar manufacturer.
Subgroups to be considered	None	None	N/A
Perspective for outcomes	All direct health effects, whether for patients or, when relevant, carers	None	Cost comparison analysis is based on costs only

Perspective for costs	NHS and personal social services	NHS and personal social services	N/A
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	3 years	Time horizon selected to reflect the assumed average treatment duration in order to capture the total costs over the period of use of the modelled therapies. The reported average (median) treatment duration with natalizumab was 3.3 years in a long-term real-world observational study.[25]
Synthesis of evidence on health effects	Based on systematic review	N/A	QALYs are not relevant to the cost comparison analysis
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults	N/A	QALYs are not relevant to the cost comparison analysis
Source of data for measurement of health-related quality of life	Reported directly by patients or carers, or both	N/A	QALYs are not relevant to the cost comparison analysis
Source of preference data for valuation of changes in	Representative sample of the UK population	N/A	QALYs are not relevant to the cost comparison analysis

health-related quality of life			
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit, expect in specific circumstances	N/A	QALYs are not relevant to the cost comparison analysis
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Costs sourced from sources reflecting prices relevant to the NHS and PSS (British National Formulary, NHS Reference Costs, Unit Costs of Health and Social Care)	N/A
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	3.5% for costs	N/A

A.6 Clinical effectiveness evidence

In contrast to new medicines, where extensive clinical data is essential for approval, biosimilars are developed and approved based on the principle of totality of evidence. This principle is based on analytical and functional comparison of the reference biologic and a biosimilar and the similarity is then verified in a smaller clinical study.

The ANTELOPE trial was a Phase 3 randomised study conducted to evaluate the efficacy, safety and immunogenicity of biosimilar natalizumab compared to reference natalizumab in patients with RRMS. A total of 264 participants were treated intravenously with either biosimilar natalizumab (n=131) or reference natalizumab (n=133) for a total of 44 weeks, with 30 patients receiving reference natalizumab switched to the biosimilar at week 24.

A.7 Key results of the clinical effectiveness evidence

The endpoints of the trial assessed the cumulative number of new active lesions on MRI imaging as well as other MRI parameters, Expanded Disability Status Scale (EDSS) score, and annualised relapse rate. The results indicated a mean difference in new lesions over 24 weeks between the two treatment arms of 0.17. As the 90% and 95% confidence intervals around this point estimate were within the prespecified upper and lower margins based on the equivalence design of the study, the primary endpoint of the study was met and equivalent efficacy was supported. Furthermore, there were no reported significant differences in secondary endpoints, safety or immunogenicity. The study concluded that the biosimilar natalizumab matched reference natalizumab in terms of efficacy, safety and immunogenicity.[26]

A.8 Evidence synthesis

As noted in Section A.2 , the most relevant comparators for biosimilar natalizumab (Tyruko) are originator natalizumab (Tysabri), ofatumumab and ocrelizumab.

The comparable efficacy of natalizumab, ocrelizumab and ofatumumab is supported by a comprehensive systematic literature review and NMA of DMTs in relapsing multiple sclerosis, published in 2023.[3] This study demonstrated comparable efficacy of natalizumab, ocrelizumab and ofatumumab on outcomes of annualised relapse rate and six month confirmed disability progression (Table 3). This NMA was based on the full trial populations rather than subgroup data for the highly active subgroup specifically; however, as noted in Section A.1 Sandoz consider this to be an appropriate framework for considering the relative efficacy of DMTs in this appraisal.

Table 3: Outcomes of published network meta-analysis supporting comparable efficacy

	Natalizumab	Ofatumumab	Ocrelizumab
Annualised relapse rate (median rate ratio with 95% CI) versus placebo	0.32 (0.23, 0.42)	0.30 (0.22, 0.41)	0.34 (0.25, 0.45)
Predefined 6-month confirmed disability progression (median	0.46 (0.30, 0.68)	0.53 (0.33, 0.87)	0.46 (0.25, 0.90)

hazard ratio with 95% CI) versus placebo			
EDSS-aligned 6-month confirmed disability progression (median hazard ratio with 95% CI) versus placebo	0.46 (0.31, 0.69)	0.48 (0.29, 0.79)	0.48 (0.27, 0.89)

Abbreviations: CI, credible interval; EDSS, Expanded Disability Status Scale.

Based on the expected comparable effectiveness of natalizumab, ocrelizumab and ofatumumab in RRMS – and by extension 'highly active' RRMS – Sandoz consider that a cost comparison would represent a proportionate approach to this evaluation and have provided a simple cost comparison analysis based on drug acquisition and administration costs within this submission (see Section A.10).

A.9 Key clinical issues

Not applicable.

A.10 Economic analysis: cost comparison

As discussed above, Sandoz considers that an appropriate and proportionate analytic framework for considering natalizumab in HA RRMS would be a cost comparison model comparing natalizumab (originator and biosimilar) against the other high-efficacy biologics that are used in clinical practice for HA RRMS patients: ocrelizumab and ofatumumab.

A cost comparison framework for this comparison is supported by a comprehensive systematic literature review and NMA of DMTs in relapsing multiple sclerosis published in 2023, which demonstrated comparable efficacy of natalizumab, ocrelizumab and ofatumumab on outcomes of annualised relapse rate and six month confirmed disability progression.[3]

The NICE positive guidance on ocrelizumab and ofatumumab is contingent on the companies providing these medicines according to simple discount patient access schemes (PAS). For on-patent molecules, stability in (discounted) pricing tends to be seen over much of the patent-protected period of the lifecycle of products subject to a NICE appraisal; hence NICE appraisals appropriately adopt list and (if relevant) PAS prices as the drug acquisition cost inputs to inform economic modelling. After loss of exclusivity and the introduction of biosimilar competition, prices become dynamic, mediated through competitive tenders, and tend to fall over time. For example, Sandoz observes that the prevailing prices for adalimumab, etanercept and infliximab are lower in 2024 than they were when TA715 was published in 2021.[20] The adapted MTA methodology applied to this appraisal and TA715 uses framework tender prices, which are inherently dynamic. Although Sandoz can neither commit to future discounts nor predict the pricing strategy of originator natalizumab (Tysabri), past experience demonstrates that there is potential for higher discounts over a much shorter time frame than the price reductions that tend to be seen for the new medicines that NICE typically assesses. Sandoz would urge NICE to consider results of any economic analyses in the context of biosimilar competition and competitive tendering for the natalizumab molecule.

Cost comparison analysis: methods

A cost comparison analysis was conducted to compare total drug acquisition and administration costs for the following therapies:

- Biosimilar natalizumab (Tyruko)
- Originator natalizumab (Tysabri) – IV formulation
- Originator natalizumab (Tysabri) – SC formulation
- Ofatumumab
- Ocrelizumab

The cost comparison analysis represented a simple analysis that considered drug acquisition and administration costs only. This was on the basis that, under an assumption of equal efficacy whereby costs associated with disease progression are not relevant to include in the comparison, the drug acquisition costs represent the most important sources of differential cost between treatments. Drug administration costs were included on the basis that there are different routes of administration and dosing schedules across the included treatments.

The cost comparison calculated average per patient costs over a time horizon of 3 years. This was on the basis that average (median) treatment duration with natalizumab was found to be 3.3 years in a long-term real-world observational study.[25] Applying a longer or shorter time horizon would not change the direction of the results, only the magnitude of cost differences between modelled interventions. Key features of the analysis are outlined in Table 4.

Table 4: Cost comparison analysis features

Time horizon	3 years	Based on median (mean not reported) treatment duration with natalizumab in the Tysabri Observational Program[25]
Discount rate	3.5%	As per NICE reference case
Perspective	NHS and social services Only drug acquisition and administration costs were included, as noted above.	As per NICE reference case

Abbreviations: NHS, National Health Service; NICE, National Institute for Health and Care Excellence.

Drug acquisition costs

The drug acquisition costs were sourced from the British National Formulary (BNF) with dosing regimens based on those in the SmPC of the respective treatments. Drug acquisition costs were calculated as an annual cost for Year 1 and then an annual cost for each subsequent year, reflecting that some treatments have a different dosing schedule in the first year of treatment.

The drug acquisition costs were calculated as per Table 5 to Table 7 below.

Drug administration costs

The drug administration costs were sourced from the 2022/2023 National Schedule of NHS Costs, where applicable. For IV administered drugs, the cost code 'AA30F – Medical care of patients with multiple sclerosis, with CC score 0-1, day case' was used, consistent with the cost code used in NICE TA533 but sourced from the latest iteration of the National Schedule of Costs (cost of £474 per administration).

For SC ofatumumab, this was assumed to be self-administered by the patient and hence require no healthcare resource use, with the exception of the requirement for an initial nurse-led training on self-administration technique. This assumption is consistent with the NICE appraisal of ofatumumab (TA699). The cost assumption for this nurse-led training session was not presented in TA699; consistent with another more recent NICE appraisal in MS (TA706), this training was assumed to require three hours of Band 7 nurse time, sourced from the latest Unit Costs of Health and Social Care manual (2023) from the Personal Social Services Research Unit (total cost of 3 hours x £62 per hour = £186).

SC-administered natalizumab cannot be self-injected by the patient as it is not supplied in an auto-injector and requires administration by a healthcare professional. Therefore, for SC natalizumab it was assumed that healthcare resource use would be required for each administration. SC administration is less time-consuming IV infusion and therefore may be expected to be associated with some cost savings per administration. The cost comparison analysis therefore tried to take this into account. The NHS Schedule of Costs does not present another code for medical care of patients with MS that represents a lower use of resource than that described above for modelling IV administration, i.e. an appropriate code from the NHS Schedule of Costs that could be used directly to represent a more simple administration could not be identified. As a simplifying assumption the cost of SC administration was therefore assumed to be the same as the cost of training a patient to self-inject that was used for ofatumumab, but this cost was applied at each administration due to the fact that patients cannot self-inject SC natalizumab and require nurse administration each time.

The resultant calculated drug administration costs are outlined in Table 8 below.

Extended interval dosing

As described earlier, some patients receiving IV natalizumab (originator or biosimilar) may use EID, whereby they receive six-weekly administrations of natalizumab rather than the standard four-weekly dose. Based on clinical opinion sought by Sandoz, in one centre in the UK approximately 25% of patients received EID dosing, reflecting those who are JCV high titre positive. Consistent with the summary of the EID in the natalizumab SmPC, clinical feedback to Sandoz indicated that EID is used after a patient has had 12–18 months on standard interval dosing.

EID was modelled for both originator natalizumab (Tysabri) IV and biosimilar natalizumab (Tyruko) IV. EID was modelled as standard (four-weekly) dosing for the first year, followed by six-weekly dosing in subsequent years. These EID IV natalizumabs were modelled as interventions in their own right, in order to transparently calculate the cost of these approaches as distinct from the standard dosing. In addition, "weighted average"

natalizumab IV interventions were modelled, based on the assumption that 25% of patients receive EID and 75% receive standard interval dosing.

Table 5: Drug acquisition costs – pack details and costs

Treatment	Concentration	Unit (vial) size (mg)	Units per pack	Cost per pack (from BNF)
Originator natalizumab (Tysabri) - intravenous	20 mg/ml	300	1	£1,130
Originator natalizumab (Tysabri) - subcutaneous	150 mg/ml	150	2	£1,130
Biosimilar natalizumab (Tyruko)	20 mg/ml	300	1	£1,017
Ofatumumab	50 mg/ml	20	1	£1,493
Ocrelizumab	30 mg/ml	300	1	£4,790

Abbreviations: BNF, British National Formulary.

Table 6: Calculated drug acquisition costs – year 1

Treatment	Dosing regimen	Units per administration	Administrations (first year)	Units required (first year)	Cost (first year)
Originator natalizumab (Tysabri)	300 mg once every 4 weeks	1	13	13	£14,690.00
Originator natalizumab (Tysabri) – EID	300 mg once every 4 weeks in Year 1 followed by 300 mg once every 6 weeks in subsequent years	1	13	13	£14,690.00
Originator natalizumab (Tysabri) – subcutaneous	300 mg once every 4 weeks	2	13	26	£14,690.00
Biosimilar natalizumab (Tyruko)	300 mg once every 4 weeks	1	13	13	£13,221.00
Biosimilar natalizumab (Tyruko) – EID	300 mg once every 4 weeks in Year 1 followed by 300 mg once every 6 weeks in subsequent years	1	13	13	£13,221.00

Ofatumumab	20 mg at weeks 0, 1 and 2 followed by subsequent monthly dosing, starting at week 4	1	15	15	£22,387.50
Ocrelizumab	Initial 300 mg dose followed by a second 300 mg dose 2 weeks later. Subsequent doses administered as a single 600 mg infusion every 6 months. The first subsequent dose should be administered 6 months after the first infusion of the initial dose.	1 or 2 (depending on dose)	3	4	£19,160.00

Abbreviations: EID, extended interval dosing.

Table 7: Calculated drug acquisition costs – each subsequent year

Treatment	Dosing Regimen	Units per Administration	Administrations (each subsequent year)	Units required (each subsequent year)	Cost (each subsequent year)
Originator natalizumab (Tysabri)	300 mg once every 4 weeks	1	13	13	£14,690.00
Originator natalizumab (Tysabri) – EID	300 mg once every 4 weeks in Year 1 followed by 300 mg once every 6 weeks in subsequent years	1	8.67	8.67	£9,793.33
Originator natalizumab (Tysabri) - subcutaneous	300 mg once every 4 weeks	2	13	26	£14,690.00
Biosimilar natalizumab (Tyruko)	300 mg once every 4 weeks	1	13	13	£13,221.00
Biosimilar natalizumab (Tyruko) – EID	300 mg once every 4 weeks in Year 1 followed	1	8.67	8.67	£8,814.00

	by 300 mg once every 6 weeks in subsequent years				
Ofatumumab	20 mg at weeks 0, 1 and 2 followed by subsequent monthly dosing, starting at week 4	1	12	12	£17,910.00
Ocrelizumab	Initial 300 mg dose followed by a second 300 mg dose 2 weeks later. Subsequent doses administered as a single 600 mg infusion every 6 months. The first subsequent dose should be administered 6 months after the first infusion of the initial dose.	2	2	4	£19,160.00

Abbreviations: EID, extended interval dosing.

Table 8: Calculated drug administration costs – first year and each subsequent year

Treatment	Dosing Regimen	Route of administration	Administration cost source	Administration cost value (per administration)	Administrations (first year)	Administration cost (first year)	Administrations (each subsequent year)	Administration cost (each subsequent year)
Originator natalizumab (Tysabri)	300 mg once every 4 weeks	Intravenous	AA30F. Medical care of patients with multiple sclerosis, with CC score 0-1. Day case as per TA533, updated to 2022/23 reference costs	£474	13	£6,162.00	13	£6,162.00

Originator natalizumab (Tysabri) – EID	300 mg once every 4 weeks in Year 1 followed by 300 mg once every 6 weeks in subsequent years	Intravenous	AA30F. Medical care of patients with multiple sclerosis, with CC score 0-1. Day case as per TA533, updated to 2022/23 reference costs	£474	13	£6,162.00	8.67	£4,108.00
Originator natalizumab (Tysabri) - subcutaneous	300 mg once every 4 weeks	Subcutaneous	3 hours of Band 7 nurse time from latest PSSRU (2023)	£186	13	£2,418.00	13	£2,418.00
Biosimilar natalizumab (Tyruko)	300 mg once every 4 weeks	Intravenous	AA30F. Medical care of patients with multiple sclerosis, with CC score 0-1. Day case as per TA533, updated to 2022/23 reference costs	£474	13	£6,162.00	13	£6,162.00
Biosimilar natalizumab (Tyruko) – EID	300 mg once every 4 weeks in Year 1 followed by 300 mg once every 6 weeks in subsequent years	Intravenous	AA30F. Medical care of patients with multiple sclerosis, with CC score 0-1. Day case as per TA533, updated to 2022/23 reference costs	£474	13	£6,162.00	8.67	£4,108.00
Ofatumumab	20 mg at weeks 0, 1 and 2	Subcutaneous	3 hours of Band 7 nurse time from latest PSSRU	£186	15	£186.00	12	£0.00

	followed by subsequent monthly dosing, starting at week 4		(2023), in alignment with approach taken in NICE TA706					
Ocrelizumab	Initial 300 mg dose followed by a second 300 mg dose 2 weeks later. Subsequent doses administered as a single 600 mg infusion every 6 months. The first subsequent dose should be administered 6 months after the first infusion of the initial dose.	Intravenous	AA30F. Medical care of patients with multiple sclerosis, with CC score 0-1. Day case as per TA533, updated to 2022/23 reference costs	£474	3	£1,422.00	2	£948.00

Abbreviations: EID, extended interval dosing; NICE, National Institute for Health and Care Excellence; PSSRU, Personal Social Services Research Unit.

Cost comparison analysis: base case results

A summary of the total costs in the first year and each subsequent year for each modelled intervention is provided in Table 9.

Table 9: Summary of annual costs – first year and each subsequent year

Treatment	Year 1			Each Subsequent Year		
	Total drug acquisition costs	Total drug administration costs	Total costs	Total drug acquisition costs	Total drug administration costs	Total costs
Originator natalizumab IV (Tysabri)	£14,690.00	£6,162	£20,852	£14,690.00	£6,162	£20,852
Originator natalizumab IV (Tysabri) – EID	£14,690.00	£6,162	£20,852	£9,793.33	£4,108	£13,901
Originator natalizumab IV (Tysabri) – weighted average	£14,690.00	£6,162	£20,852	£13,465.83	£5,649	£19,114
Originator natalizumab (Tysabri) - subcutaneous	£14,690.00	£2,418	£17,108	£14,690.00	£2,418	£17,108
Biosimilar natalizumab IV (Tyruko)	£13,221.00	£6,162	£19,383	£13,221.00	£6,162	£19,383
Biosimilar natalizumab IV (Tyruko) – EID	£13,221.00	£6,162	£19,383	£8,814.00	£4,108	£12,922
Biosimilar natalizumab IV (Tyruko) – weighted average	£13,221.00	£6,162	£19,383	£12,119.25	£5,649	£17,768
Ofatumumab	£22,387.50	£186	£22,574	£17,910.00	£0	£17,910

Ocrelizumab	£19,160.00	£1,422	£20,582	£19,160.00	£948	£20,108

Abbreviations: EID, extended interval dosing; IV, intravenous.

The results of the cost comparison analysis over the 3 year time horizon and applying a 3.5% annual discount rate as per the NICE reference case are outlined in Table 10. All treatments are included at list price as per the price listed on the BNF.

Table 10: Base case results – list price

Treatment	Total drug acquisition costs	Total drug administration costs	Total costs
Originator natalizumab IV (Tysabri)	£41,156	£17,264	£58,420
Originator natalizumab IV (Tysabri) – EID	£32,168	£13,494	£45,662
Originator natalizumab IV (Tysabri) – weighted average	£38,909	£16,321	£55,230
Originator natalizumab (Tysabri) - subcutaneous	£41,156	£6,774	£47,930
Biosimilar natalizumab IV (Tyruko)	£37,040	£17,264	£54,304
Biosimilar natalizumab IV (Tyruko) – EID	£28,952	£13,494	£42,445
Biosimilar natalizumab IV (Tyruko) – weighted average	£35,018	£16,321	£51,339
Ofatumumab	£54,503	£180	£54,683
Ocrelizumab	£53,679	£3,114	£56,793

Abbreviations: EID, extended interval dosing; IV, intravenous.

[redacted]

Table 11: Base case results – discounted price

Treatment	Total drug acquisition costs	Total drug administration costs	Total costs
Originator natalizumab IV (Tysabri)	£41,156	£17,264	£58,420
Originator natalizumab IV (Tysabri) – EID	£32,168	£13,494	£45,662
Originator natalizumab IV (Tysabri) – weighted average	£38,909	£16,321	£55,230
Originator natalizumab (Tysabri) - subcutaneous	£41,156	£6,774	£47,930
Biosimilar natalizumab IV (Tyruko)	[redacted]	[redacted]	[redacted]
Biosimilar natalizumab IV (Tyruko) – EID	[redacted]	[redacted]	[redacted]
Biosimilar natalizumab IV (Tyruko) – weighted average	[redacted]	[redacted]	[redacted]
Ofatumumab	£54,503	£180	£54,683
Ocrelizumab	£53,679	£3,114	£56,793

Abbreviations: EID, extended interval dosing; IV, intravenous.

Cost comparison analysis: summary of findings

The modelled treatments are associated with similar total costs in this simple cost comparison analysis based on drug acquisition and administration costs. The analysis finds that when considering the potential for EID, at list price IV biosimilar natalizumab is associated with slightly lower total costs than all other comparators.

It is also important to maintain awareness that prices in markets where biologic and biosimilars compete tend to fall over time. This contrasts with the commercial context for new, on-patent only medicines that are more commonly appraised by NICE. Results of economic analyses should be considered in this context, including in relation to considering the cost comparison of biosimilar natalizumab IV and originator natalizumab SC, given that the acquisition prices of both Tyruko and Tysabri are inherently more dynamic due to the competitive tendering environment.

When factoring the confidential discount for biosimilar natalizumab, the total costs are lowest with biosimilar natalizumab; however, this analysis is unable to incorporate any discounts that may be available for comparator products.

Overall, this simple analysis based on an assumption of equivalent efficacy versus the relevant comparators in highly active disease supports the economic case for recommending biosimilar natalizumab in this population.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple sclerosis (relapsing, remitting, highly active) – natalizumab and Tyruko (biosimilar natalizumab) (after disease modifying therapy) [ID6369]

Sandoz Ltd

Biosimilar natalizumab (Tyruko)

Summary of Information for Patients (SIP)

August 2024

File name	Version	Contains confidential information	Date
Natalizumab ID6369 [noCON] Sandoz Summary of Information for Patients v1.1 FINAL	V1.1	No	28/08/2024

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

SECTION 1: Submission summary

1a) Name of the medicine (generic and brand name):

Response:

Generic name: Biosimilar natalizumab

Brand name: Tyruko

1b) Population this treatment will be used by. Please outline the main patient population that is being appraised by NICE:

Response:

The population that this treatment is being appraised for is patients with relapsing-remitting multiple sclerosis who have highly active disease despite a full and adequate course of treatment with at least one disease modifying therapy.

Relapsing-remitting multiple sclerosis is the most common form of multiple sclerosis and is characterised by periods of flare-ups (relapse), between which there are periods of recovery (remission). This appraisal relates specifically to patients who have a highly active form of the disease, which is defined by the patient still suffering from the condition despite having tried a full and adequate course of at least one previous therapy that had the potential to treat the disease by reducing flare-ups and slowing progression.

1c) Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

Response:

Tyruko has a marketing authorisation from the Medicines and Healthcare products Regulatory Agency (MHRA) for the treatment of two groups of patients with relapsing-remitting multiple sclerosis:

- Patients with highly active disease despite a full and adequate course of treatment with at least one disease modifying therapy (DMT) – **this is the part of the marketing authorisation that is being considered in this appraisal**

- Patients with rapidly evolving severe RRMS defined by 2 or more disabling relapses in one year, and with 1 or more Gadolinium enhancing lesions on brain Magnetic Resonance Imaging (MRI) or a significant increase in T2 lesion load as compared to a previous recent MRI – **natalizumab is already recommended by NICE in this part of the marketing authorisation, so this is not relevant to the current appraisal**

Details of the regulatory approval for Tyruko can be found here

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

Response:

Corporate supporter of the Neurological Alliance

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

Response:

The symptoms of multiple sclerosis vary from patient to patient and each individual may experience some or none of them. They may include, for example: walking problems, numbness in the face, arms or legs, problems with vision, tiredness, lack of balance, difficulty thinking and concentrating, depression, pain, stiffness and muscle spasms.

Where symptoms flare up this is called a relapse and the patient may notice their symptoms suddenly, within a few hours, or progressing slowly over the course of several days.

Symptoms then usually gradually improve for a period (known as a period of remission) before the next flare-up.

Multiple sclerosis is a progressive disease, meaning that over time the disease worsens and the flare-ups can become more frequent and more debilitating, ultimately leading to a higher burden of disability. In more progressed stages of the disease this can pose a considerable health burden on the patient and also lead to the need for significant support from carers, such as family members.

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?
Response: Diagnosis of relapsing-remitting multiple sclerosis is based on identification of a pattern of symptoms consistent with the disease and then confirmed via brain imaging scans, such as MRI. Symptoms can sometimes be vague or similar to other conditions, so a GP will refer patients to a neurologist for specialist assessment if multiple sclerosis is suspected.

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed: • What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP. • Please also consider: o if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data. o are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.
Response: There are a number of treatments available for patients with relapsing-remitting multiple sclerosis. Available treatments do not only treat the symptoms of the disease but are also able to slow the progression of the disease and reduce the number of flare-ups (relapses) with varying levels of effectiveness – these treatments are therefore known as disease-modifying therapies (DMTs). The DMT that a patient is prescribed will be dependent on what the clinician and their patient considers most appropriate for their disease. Different DMTs have different levels of effectiveness and also different side-effects, so the choice of DMT will consider the balance of benefit and risk that is best for the patient. Natalizumab is generally considered to be a “high efficacy” (i.e. highly effective) DMT, as per the guidelines from the Association of British Neurologists.[1] This NICE appraisal is focused on considering whether natalizumab should be made available to patients after their treatment with a previous DMT has not worked successfully.

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

Response: No PBE has been collected to inform this summary.

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

Response:

Natalizumab is a biological medicine (a “biologic”), meaning that rather than being a chemical compound created through chemical processes (as is the case for a typical tablet) it is a more complex molecule (specifically a protein molecule) and is made from living cells.

The way in which natalizumab works against relapsing-remitting multiple sclerosis is not fully understood. Natalizumab is believed to work by blocking a patient’s own immune cells (white blood cells) from crossing into the patient’s central nervous system and mistakenly attacking their own nerves. By keeping the immune cells in the bloodstream and blocking them entering the central nervous system, natalizumab can help to reduce damage to nerve cells.[2]

The first version of a biological medicine is known as the “reference” or “originator” product; The reference product for natalizumab is called Tysabri. The reference product takes many years of research to develop. Once developed, patents are the protection held by a pharmaceutical company so that only it is allowed to make the medicine. Once this expires, different companies can make a biosimilar version.

Tyruko is a biosimilar version of natalizumab. A biosimilar is a copy of an approved reference biological medicine. It is equivalent to the reference medicine in terms of safety and efficacy. Biosimilars go through detailed studies comparing them to the reference biological medicine and are then approved by the MHRA before they are made available for use. Patients can therefore expect the same outcomes using a biosimilar as they

would with the reference product. Biosimilars can be more cost-effective than their reference medicine, because the significant investment into clinical research has already been made. This may improve patient access to biologic treatments, as was the case in rheumatoid arthritis, where the onset of biosimilars meant access to biologic treatment could be expanded to patients with moderate in addition to only severe cases of the disease.

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

- Yes / No

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

Response: No, Tyruko is not intended to be used in combination with other medicines.

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

Response:

Tyruko should be administered as a 300 mg dose by intravenous infusion once every 4 weeks. Patients will need to go to the hospital every 4 weeks so that a nurse can administer the treatment for them by delivering the treatment in its liquid form into the patient's bloodstream via an intravenous drip.

Some patients may be able to use 'extended interval dosing', meaning that they only need to have an administration of Tyruko every 6 weeks rather than every 4 weeks.

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.
Response: The ANTELOPE trial was a Phase 3 study conducted to evaluate the efficacy, safety and immunogenicity (the extent to which the patient's immune system may react adversely to the drug) of biosimilar natalizumab compared to reference natalizumab in patients with relapsing-remitting multiple sclerosis.[3] A total of 264 participants were treated intravenously with either biosimilar natalizumab (n=131) or reference natalizumab (n=133) for a total of 44 weeks, with 30 patients receiving reference natalizumab switched to the biosimilar at week 24.The study was designed to demonstrate the equivalence of biosimilar natalizumab and reference natalizumab with regards to various measures of disease activity, such as rate of relapses, presence of lesions and level of disability. The results of the study supported the conclusion of equivalent efficacy of biosimilar natalizumab and reference natalizumab and this study led to biosimilar natalizumab (Tyruko) receiving a marketing authorisation. Other studies of biosimilar natalizumab have also been studied that provide further support for the efficacy and safety of this treatment for patients. In contrast to new medicines, where extensive clinical data is essential for approval, biosimilars are developed and approved based on the principle of totality of evidence. This principle is based on analytical and functional comparison of the reference biologic and a biosimilar and the similarity is then verified in a smaller clinical study.

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition. In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.
Response: Please see the summary above. Biosimilar natalizumab (Tyruko) provides equivalent efficacy to that of reference natalizumab (Tysabri).

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs).** Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.
Response: The evidence for biosimilar natalizumab is based on the equivalence study (ANTELOPE) described above, which supports that the benefits of biosimilar natalizumab (Tyruko) on patients will be as per reference natalizumab (Tysabri).

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer. Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.
Response: The safety profile of natalizumab biosimilar (Tyruko) is expected to be the same as for the reference natalizumab (Tysabri) administered intravenously.

3h) Summary of key benefits of treatment for patients

Issues to consider in your response: • Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments. • Please include benefits related to the mode of action, effectiveness, safety and mode of administration •
Response: The key benefit of biosimilar natalizumab (Tyruko) above and beyond the benefits of reference natalizumab (Tysabri) is that it provides the efficacy and safety profile (and hence clinical value) of reference natalizumab but at a lower drug acquisition cost. Cost-effective use of resources and achievement of cost savings are important for the NHS and for patients because these savings can be reinvested to improve patient services, for

example by funding new medicines or diagnostic tool, or increasing numbers of healthcare professionals such as nurses.

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

Response:

Biosimilar natalizumab (Tyruko) is associated with the same disadvantages as the intravenous form of reference natalizumab (Tysabri) in terms of side-effects and the burden on patients of needing to travel to hospital every 4 weeks for treatment administration. A subcutaneously administered formulation of Tyruko is not available.

3i) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

Response:

The Sandoz submission to NICE for this technology appraisal provided a simple economic analysis called a cost comparison. This analysis assumed the same efficacy of biosimilar natalizumab (Tyruko), reference natalizumab (Tysabri) and the other 'high efficacy' biologic treatments (ofatumumab and ocrelizumab) and hence compared only the costs of these different treatments. The costs included in the simple analysis were drug acquisition and administration costs and these costs were modelled over an assumed treatment duration of 3 years. In this analysis performed by Sandoz, biosimilar natalizumab (Tyruko) was associated with lower total costs than reference natalizumab (Tysabri) administered intravenously, as would be expected based on the lower drug acquisition cost of the biosimilar.

It should be noted that in cases where there are competing biosimilar products and reference products, drug prices may fall over time and hence reduce total costs of treatments for the NHS.

3j) Innovation

NICE considers how innovative a new treatment is when making its recommendations.

If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

Response:

Biological medicines are currently the largest cost and cost growth areas in the NHS medicines budget.[4] As such, "using best value biologic medicines in line with NHS England commissioning recommendations" is one of NHS England's sixteen national medicines optimisation opportunities for the NHS in 2023/2024 and the NHS endeavours

to treat 90% of new patients with the best value biologic medicine within 3 months of guidance being issued. [4,5]

Biosimilar natalizumab offers an opportunity to support the potential identified by the NHS to deliver savings of up to £300m each year through use of biosimilars, enabling more patients to have access to other life-saving and life-enhancing treatments.[4]

3k) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.

Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics

More information on how NICE deals with equalities issues can be found in the NICE equality scheme

Find more general information about the Equality Act and equalities issues here

Response: Not applicable

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc.
Where possible, please provide open access materials or provide copies that patients can access.

Response:

- **MS Society summary of relapsing-remitting multiple sclerosis:** https://www.mssociety.org.uk/about-ms/types-of-ms/relapsing-remitting-ms

- **Association of British Neurologists clinical guidelines for multiple sclerosis:** https://api.repository.cam.ac.uk/server/api/core/bitstreams/66c5edad-012c-411a-9e21-7cb7425e7875/content
- **Description of potential mechanism of action of natalizumab:** https://www.tysabri.com/en_us/home/about/how-tysabri-may-work.html
- **NHS explanation on biosimilars:** https://www.england.nhs.uk/long-read/what-is-a-biosimilar-medicine/#:~:text=Biological%20medicines%20are%20used%20to,known%20as%20the%20reference%20product.
- **Tyruko summary of product characteristics and patient information leaflet from the MHRA:** https://products.mhra.gov.uk/search/?search=tyruko&page=1
- **Clinical publication for the Antelope study of Tyruko:** https://jamanetwork.com/journals/jamaneurology/fullarticle/2800332

Further information on NICE and the role of patients**:**

- Public Involvement at NICE Public involvement | NICE and the public | NICE Communities | About | NICE
- NICE's guides and templates for patient involvement in HTAs Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector (VCS) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE
- EUPATI guidance on patient involvement in NICE: https://www.eupati.eu/guidance-patient-involvement/
- EFPIA – Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf
- National Health Council Value Initiative. https://nationalhealthcouncil.org/issue/value/
- INAHTA: http://www.inahta.org/
- European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

4b) Glossary of terms

Response: Terms have been explained in the preceding text as required.

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

Response:

1. Scolding N, Barnes D, Cader S, et al. Association of British Neurologists: revised (2015) guidelines for prescribing disease-modifying treatments in multiple sclerosis. *Pract Neurol*. Aug 2015;15(4):273-9. doi:10.1136/practneurol-2015-001139

2. The Science Behind Tysabri. Available from: https://www.tysabri.com/en_us/home/about/how-tysabri-may-work.html. [Last Accessed: 12th August 2024.].

3. Hemmer B, Wiendl H, Roth K, et al. Efficacy and Safety of Proposed Biosimilar Natalizumab (PB006) in Patients With Relapsing-Remitting Multiple Sclerosis: The Antelope Phase 3 Randomized Clinical Trial. *JAMA Neurol*. Mar 1 2023;80(3):298-307. doi:10.1001/jamaneurol.2022.5007

4. NHS England. Commissioning framework for biological medicines (including biosimilar medicines). 2017;

5. NHS England. National medicines optimisation opportunities 2023/24. 2023. Available from: https://www.england.nhs.uk/long-read/national-medicines-optimisation-opportunities-2023-24/. [Last Accessed: 21st February 2024].

This proposal has been developed and funded by Sandoz Limited UK following discussion and guidance from five UK clinical experts in MS under a consultancy agreement. The clinical cases were provided by the expert group.

SANDOZ

Biosimilar natalizumab: opportunities for early and equitable access to natalizumab in England

Executive summary

This proposal document has been written by Sandoz based on guidance from a group of five clinical experts in multiple sclerosis, practicing in the UK (the expert group). Two 2-hour meetings were held with the expert group in July and August 2023 to advise on the document. Following these meetings, The expert group reviewed and amended the drafts, provided the case studies and approved the final version of the document.

The introduction of biosimilar natalizumab means that this highly effective disease modifying therapy (DMT) will soon be available to the NHS at a reduced cost compared with the originator natalizumab (Tysabri). This presents an opportunity to revisit the historical NICE assessment and the current NHSE algorithm. Cost modelling in line with the methodology used by NICE is available from Sandoz on request.

Natalizumab was last assessed by NICE in 2007 at a time when natalizumab was the only highly effective DMT for MS and there was no modern comparator available for a cost comparison [see Natalizumab populations for more details]. In that appraisal, natalizumab was approved for the treatment of rapidly evolving severe (RES) RRMS, defined by 2 or more disabling relapses in 1 year, and one or more gadolinium-enhancing lesions on brain magnetic resonance imaging (MRI) or a significant increase in T2 lesion load compared with a previous recent MRI.[1,2]

A second group of patients, for which natalizumab is licensed, was not approved by NICE on the basis of cost and clinical study design: Patients with high disease activity despite treatment with beta interferon. NICE referred to this group as the 'suboptimal therapy group'.[2] In the natalizumab licence, this indication was reworded in 2016 to: Patients with highly active disease despite a full and adequate course of treatment with at least one DMT.[1]

Since 2007, the treatment landscape in MS has changed with the introduction of several high-efficacy, and high cost, DMTs. Treatment paradigms have changed with widespread, early use of high efficacy therapies. In addition, the clinical experience and evidence for natalizumab's efficacy and safety have grown to include long-term real-world evidence across all populations indicated in the licence [see Background on natalizumab for details].

Sandoz has been engaged in discussions with NICE since June 2022 and, despite efforts by both parties, it has proven challenging to identify the appropriate route for appraisal of biosimilar natalizumab as there is currently no NICE process that fits the situation perfectly. In Sandoz's understanding this could potentially be achieved via a commissioning policy Care Programme Approach (CPA) process. Sandoz continues to work with NICE to establish how existing methods may be adopted but in parallel, Sandoz and the expert group suggest that NHS England (NHSE) considers independently updating its algorithm and the Blueteq form to align access to natalizumab with the licence. [see Proposal].

There are precedents for NHSE acting independently from NICE based on patient needs and the availability of additional clinical evidence (siponimod and fingolimod). NHSE also took the decision to expand access to

natalizumab during the COVID-19 pandemic to include all patients within the product licence, which led to a 46.9% increase in the number of initiations in 2020 compared with 2019.[3]

The current regulations on natalizumab prescribing in England mean that patients who are currently suboptimally treated for their MS may not be able to access natalizumab, despite the fact that more than 10 years of evidence suggests they may benefit from this treatment, and despite the fact that for additional clinical reasons this may be the best choice of DMT for their clinical circumstance [see Case studies provided by the expert group]. This UK situation is different from other countries where natalizumab is prescribed as per the licensed indication. Clinical trials and real-world observational studies demonstrate that early (within 2 years from disease onset) use of high-efficacy DMTs, including natalizumab, results in improved long-term outcomes for people with MS, including reduced disability worsening, reduced annualised relapse rate (ARR) and enhanced quality of life.[4,5,6,7,8] Reviewing the regulations on natalizumab use may enable more people with MS to benefit from a high efficacy treatment at an early stage of their disease.

Thank you for considering our proposal and please let us know if we can provide further information to help with your decisions.

From Sandoz Medical Affairs and the expert group

The expert group *is comprised of MS specialists practicing in England representing the perspective of consultant neurologists, nurses and pharmacists, brought together by Sandoz to advise on the development of this proposal document.*

- *Wallace Brownlee, Consultant Neurologist and Honorary Associate Professor of Neurology, Queen Square Multiple Sclerosis Centre, National Hospital for Neurology and Neurosurgery*
- *Rachel Dorsey-Campbell, Senior Lead Pharmacist Neurosciences, Imperial College Healthcare NHS Trust*
- *David Paling, Consultant Neurologist, Royal Hallamshire Hospital in Sheffield, and Doncaster Royal Infirmary*
- *Waqar Rashid, Consultant Neurologist, St Georges Hospital NHS Foundation Trust*
- *Ruth Stross, Head of Nursing/ MS Specialist Nurse Advisor, Neurology Academy*

In addition to the expert group, the final version of this proposal document was reviewed and endorsed on behalf of the following expert professional bodies.

- *Association of British Neurologists (ABN) - Special interest group for MS and neuroinflammation*
- The *Multiple Sclerosis Academy*, part of the Neurology Academy, an education provider for clinicians, specialist nurses and professional allied to medicine
- The UK *MS Specialist Nurse Association* (MSSNA), a professional organisation for MS nurses in the UK

Supporting information appendices

1. Natalizumab populations: current NHSE algorithm vs licensed indication

NICE assessed natalizumab in 2007 in two groups of patients as per the licensed indication at the time:[2]

	Natalizumab is indicated as single DMT in adults with highly active RRMS for the following patient groups[1]	
NICE/NHSE position[2]	**Original indication in 2007[2]**	**Current indication since 2016[1]**
Suboptimal therapy group [NICE terminology]: Not recommended	Patients with high disease activity despite treatment with beta interferon. This group is defined as patients who have failed to respond to a full and adequate course of a beta interferon. Patients should have had at least one relapse in the previous year while on therapy, and have at least nine T2-hyperintensive lesions in cranial MRI or at least one gadolinium-enhancing lesion	Patients with highly active disease despite a full and adequate course of treatment with at least one DMT
RES group [NICE & NHSE terminology]: Recommended	Patients with RES RRMS defined by 2 or more disabling relapses in 1 year, and with one or more gadolinium-enhancing lesions on MRI or a significant increase in T2 lesion load as compared to a previous recent MRI	Unchanged

Data from two clinical trials were available to NICE in 2007:

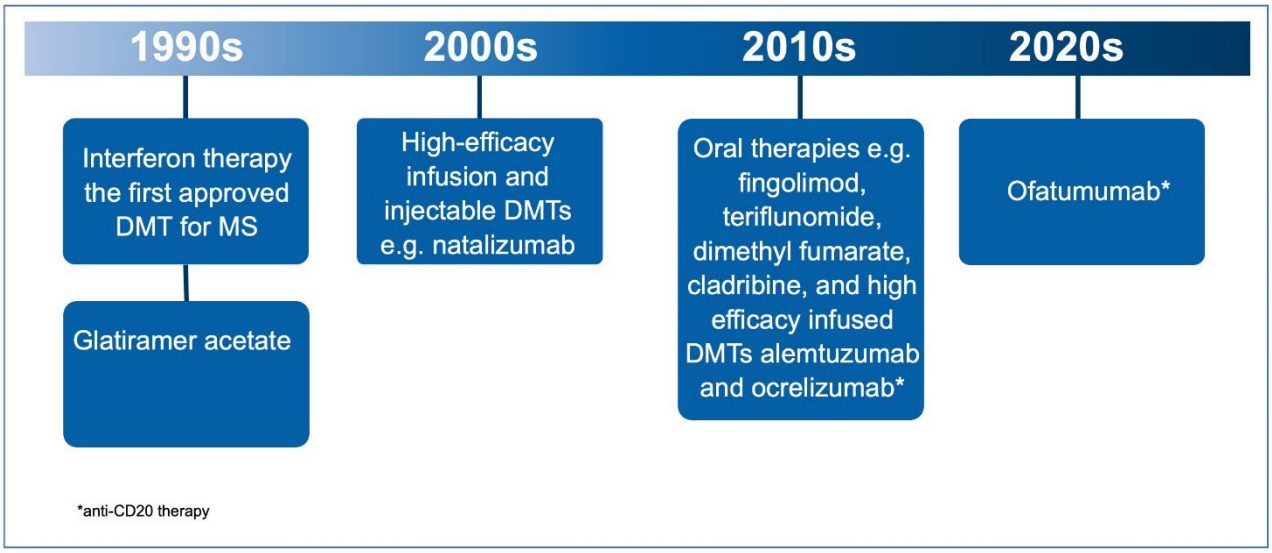
- The multinational, double-blind, randomised AFFIRM study (N=942), which compared natalizumab with placebo. The study comprised people with RRMS, of which a subgroup had highly active RRMS. A *post hoc* subgroup analysis of AFFIRM (n=209) provided clinical data for the RES group in the NICE technology appraisal.
- The marketing authorisation for what NICE called the 'suboptimal therapy group' was based on data from the SENTINEL study (N=1171), which compared natalizumab and beta interferon with beta interferon alone. However, the combination of natalizumab with beta interferon is not included in the marketing authorisation for natalizumab because of concerns over the risk of progressive multifocal leukoencephalopathy (PML), and data from the SENTINEL study were not presented to NICE by the manufacturer. Instead, the manufacturer assumed that the intention to treat (ITT) population from AFFIRM was a suitable proxy for the 'suboptimal therapy group'.

Since 2007, extensive real-world evidence has been generated illustrating the long-term disease control achieved with natalizumab. Current European guidelines and the ABN guidelines recommend natalizumab as per the licence without restricting it to the RES group.[9,10]

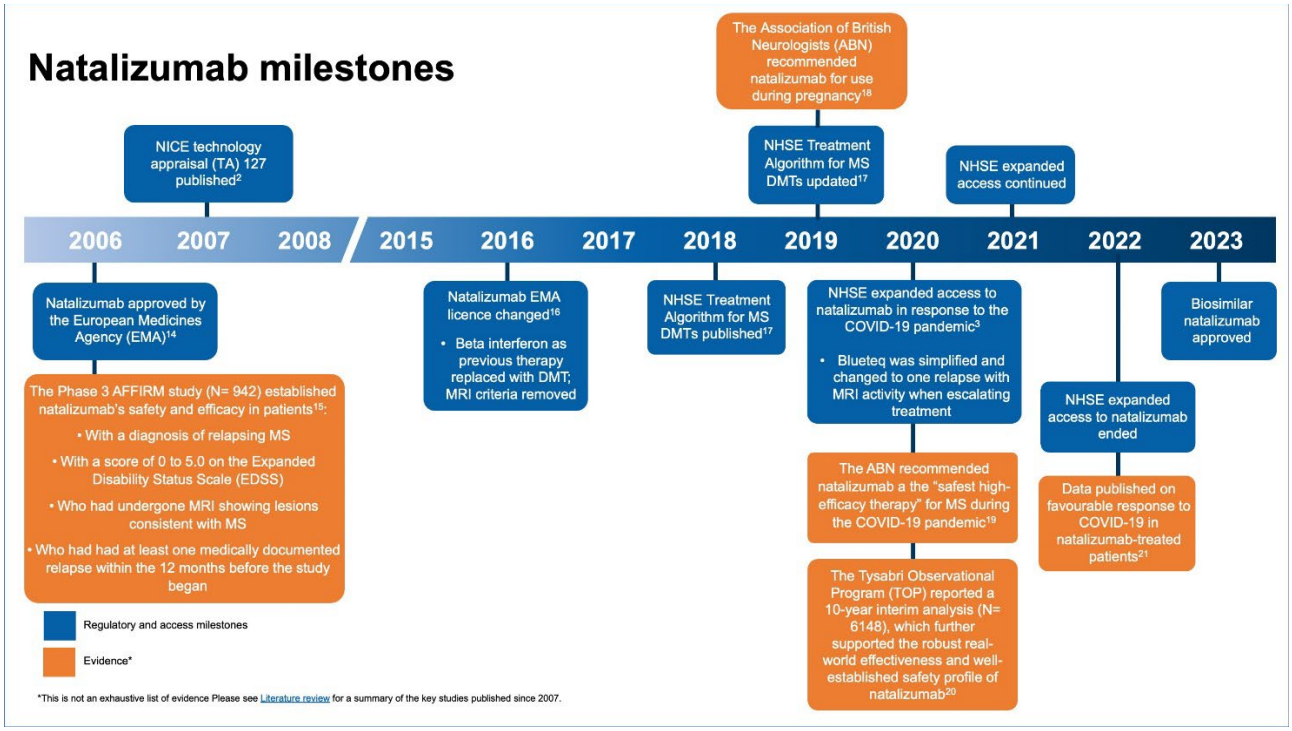
2. Background on natalizumab

The introduction of DMTs such as natalizumab has transformed outcomes for patients with highly active RRMS.

Timeline of MS therapeutic approaches[11,12,13]



Natalizumab milestones[14,15,16,17,18,19,20,21]



*This is not an exhaustive list of evidence Please see Literature review for a summary of the key studies published since 2007.

Biosimilar natalizumab

Biosimilar natalizumab has been approved by The Medicines and Healthcare products Regulatory Agency (MHRA) based on equivalence to originator natalizumab evidenced by the ANTELOPE study.[22]

A comparable John Cunningham virus (JCV)-testing service to originator natalizumab will be provided by Sandoz.

Patient support will be provided by Sandoz for those prescribed biosimilar natalizumab.

Biosimilar natalizumab is available to the NHS at a lower cost than originator natalizumab and other high-efficacy DMTs, which completely changes the 2007 NICE cost analysis and the resulting decisions made by NHSE to limit access to one aspect of the full licence for natalizumab.

Given the experience with other biosimilars and generics across therapy areas, it is likely that NHSE will prioritise the use of biosimilar natalizumab over the branded originator natalizumab to mitigate the overall increasing cost of MS therapies as a whole. This presents an opportunity for NHSE to expand access to natalizumab with minimal overall budgetary impact.

Sandoz is already working with healthcare professionals in England to understand and help address any organisational requirements to ensure smooth uptake of biosimilar natalizumab, where appropriate, in practice.

3. Proposal for biosimilar natalizumab prescribing in NHSE

Limitations of the current NHSE algorithm

The NHSE algorithm and Blueteq form derive from the now outdated 2007 NICE technology appraisal of natalizumab. In the intervening 16 years, new evidence has emerged that alters the clinical and cost effectiveness analysis that was performed:

- Extensive new clinical evidence has been generated about the long-term efficacy and safety of natalizumab in the licensed indications
- The indication for what NICE called the 'suboptimal therapy group' was changed in 2016 in the natalizumab summary of product characteristics (SPC)
- The cost-effectiveness model reviewed by NICE has radically changed given the introduction of biosimilar natalizumab

Proposed new NHSE algorithm

We recommend that the full licensed indications for natalizumab are represented in the NHSE algorithm,[17] allowing patients access to this treatment as an alternative to other highly-effective DMTs that are more immunosuppressive, such as anti-CD20s (ocrelizumab, ofatumumab) or ponesimod.

Therefore, in addition to its current position for the first-line treatment of RES MS, natalizumab should be listed in the NHSE algorithm as a treatment option of RRMS for *patients with highly active disease despite a full and adequate course of treatment with* ***at least one disease modifying therapy (DMT)*** *aligned with natalizumab's current licence.*[1]

Limitations of the current Blueteq form

The current Blueteq form for natalizumab is shown below.

Please indicate whether patient meets the following criteria:	Please tick
1. I confirm the patient has a diagnosis of rapidly evolving severe (RES) relapsing-remitting multiple sclerosis as defined in NICE TA 127	○ Yes ○ No * Required
2. I confirm that the patient has had two or more disabling relapses in the past year	○ Yes ○ No * Required
3. I confirm the patient meets ONE of the following criteria: ○ The patient has one or more gadolinium-enhancing lesions on MRI ○ The patient has a significant increase in T2 lesion load compared with previous MRI* ○ A comparator MRI is unavailable or assessment of gadolinium-enhancement is unreliable as the patient was treated with steroids at around the time of scan. * Required ***at least three months apart with the first MRI undertaken no more than 3 years ago**	○ Yes ○ No * Required

Proposed new Blueteq form

Please indicate whether patient meets the following criteria:	Please tick
1. I confirm that the patient meets one of the following criteria: O The patient has highly active disease despite a full and adequate course of treatment with at least one disease modifying therapy (DMT) O The patient has rapidly evolving severe (RES) RRMS defined by 2 or more disabling relapses in 1 year, and with one or more gadolinium-enhancing lesions on brain magnetic resonance imaging (MRI) or a significant increase in T2 lesion load as compared with a previous recent MRI • OR a comparator MRI is unavailable or assessment of gadolinium-enhancement is unreliable as the patient was treated with steroids at around the time of scan * Required	O Yes O No * Required

4. Case studies

The expert group has provided the following cases from their own practices that are illustrative of the types of patients who are currently denied access to natalizumab, either due to the NHSE algorithm or because of variations in interpretation of the criteria, but whom they feel have evidence-based reasons to benefit from this treatment.

4.1 Patients planning a pregnancy or currently pregnant
4.2 Patients at high risk of exposure to infection
4.3 Patients for whom anti-CD20 agents are inappropriate
4.4 Patients with low lymphocytes following previous DMT

4.1. Patients planning a pregnancy or currently pregnant

Case study provided by Rachel Dorsey-Campbell, Senior Lead Pharmacist Neurosciences, Imperial College Healthcare NHS Trust

MS is more than twice as common in females than males (England data: 272 female versus 106 male per 100,000 population).[23] Since the condition is most often diagnosed in early adulthood, many patients will not have completed their families at the time of diagnosis. There is increasing awareness of the importance of early treatment in preventing long-term disability in MS. Delaying treatment until women with MS have completed their families can lead to the development of irreversible disability.[18]

The SPC is clear about the use of natalizumab in pregnancy: "This drug should be used during pregnancy only if clearly needed. If a woman becomes pregnant while taking natalizumab, discontinuation of natalizumab should be considered."[1] However, its use in pregnancy is supported by ABN guidelines to provide a potential alternative to women being untreated during this time.[18]

Case study	**Current situation**
• 35 year old female school teacher, diagnosed with RRMS 3 years ago • Started on Interferon 2 years ago • 2 recent significant relapses prompting discussion about treatment escalation; recent MRI is stable but treatment can be offered on clinical activity alone • She is offered fingolimod, ponesimod, ofatumumab or ocrelizumab in line with the current NHSE algorithm • During consultation with her MS nurse, she explains that she has recently got married and would like to start a family in the near future and is actively trying to conceive	• Fingolimod and siponimod are contraindicated in a woman who is trying to conceive • Ocrelizumab and ofatumumab could be started but advice would be for her to be on treatment for at least 6 months and then wait at least 3 months after her last dose before trying to conceive. This would require her to delay her plans to conceive by 9–12 months. She is already 35 years of age and concerned about her fertility • This lady fits the licenced indication for natalizumab: Patients with highly active disease despite a full and adequate course of treatment with at least one DMT[1] • However she is not able to access natalizumab as she is not defined as having RES MS, having not had changes on her MRI scan • She is therefore likely to remain suboptimally treated with interferon while she tries to conceive, increasing her risk of disease activity and accrual of disability[18]
Expert group assessment: • The ABN recommended that natalizumab is an effective option for use during pregnancy.[18]	
Expert group recommendation: If there is a clear need for DMT for a patient who is considering pregnancy or is pregnant, natalizumab should be considered as an option, taking into account the relevant information in the SPC	

4.2. Patients at high risk of exposure to infection

Case study provided by Wallace Brownlee, Consultant Neurologist and Honorary Associate Professor of Neurology, Queen Square Multiple Sclerosis Centre, National Hospital for Neurology and Neurosurgery

The COVID-19 pandemic highlighted the need to provide people who have long-term conditions with continuing care that maximises their health and minimises their risk of infection. While the COVID-19 pandemic is over, there may be other pandemics in the future and with or without a pandemic there are individuals who are at increased risk of exposure to infection every day.

Those working in healthcare settings are the most obvious of such populations. There are also patients with MS and a comorbidity such as inflammatory bowel disease or other systemic diseases, who are being treated with immunosuppressive therapies. Since natalizumab is not immunosuppressive,[3] it can be considered as a safer option than immunosuppressive DMTs for MS in these patients, thus addressing the patient's the overall infection risk.

Case study	**Current situation**

• A 41 year old patient with relapsing MS works as an advanced nurse practitioner in a GP practice
• She has recently had a disabling relapse while taking treatment with dimethyl fumarate and a repeat MRI scan showed 2 new brain lesions
• Her neurologist recommends escalation of her treatment to ocreliuzmab or ofatumumab
• She is worried about the increased risk of infections with anti-CD20 agents and impaired vaccine responses given her occupational exposure to COVID-19 and other respiratory infections
	• This patient is not classed as RES RRMS eligible for natalizumab because she has not had **2 or more relapses in the last year**
	• This patient is included in the current indication for natalizumab as part of what NICE refers to as the 'suboptimal therapy group':
	  ○ Patients with highly active disease despite a full and adequate course of treatment with at least one DMT
	  ○ However, natalizumab is not recommended by NICE for this group and natalizumab is not permitted under NHSE/Blueteq
	• This patient is currently only eligible for:
	  ○ Ofatumumab
	  ○ Ocrelizumab
	  ○ Ponesimod
	  ○ Stem cell transplantation in a trial

Expert group assessment: • The current NICE technology appraisal from 2007, which did not approve natalizumab for use in the 'suboptimal therapy group', is based on the old definition rather than the current natalizumab licensed indication:[2] ○ Patients with high disease activity despite treatment with beta interferon. This group is defined as patients who have failed to respond to a full and adequate course of a beta interferon. Patients should have had at least one relapse in the previous year while on therapy, and have at least nine T2-hyperintensive lesions in cranial MRI or at least one gadolinium-enhancing lesion • NHSE has accepted that natalizumab is a preferred option in patients at risk of infection as evidenced by its expanded access initiative during the COVID-19 pandemic[3]	
Expert group recommendation: Natalizumab would be a preferred option for any patient who is concerned about infection, or taking concomitant immunosuppressive drugs for another condition, and is JCV-negative Note: The physician has must confirm that such patients are not immunocompromised before starting natalizumab treatment[1]	

4.3. Patients for whom anti-CD20 agents are inappropriate

Case study provided by David Paling, Consultant Neurologist, Royal Hallamshire Hospital in Sheffield, and Doncaster Royal Infirmary

Anti-CD20 monoclonal antibodies selectively deplete CD20+ B and CD20+ T cells and efficiently suppress inflammatory disease activity.[24] Due to their mechanism of action, anti-CD20 antibody therapies may be associated with an increased risk of infections. Evidence suggests that the risk of severe infection is associated with comorbidities, higher age, longer duration of treatment, and higher EDSS scores.[25]

Case study	**Current situation**
• 43 year old woman with RRMS who works • Her initial symptoms were in 2014 and she was diagnosed in 2015 • She was started on dimethyl fumarate in 2016 • She initially did well on dimethyl fumarate, but after 4 years she had a new lesion on MRI, followed by a clinical relapse the following year • She was in the process of considering a change in treatment when she was diagnosed with breast cancer • She had a lumpectomy and chemotherapy in 2022 • She would like to escalate her treatment but her oncologist warns against the use of anti-CD20 therapies (ocrelizumab and ofatumumab) in view of their association with higher rates of breast cancer[26]	• Despite having a relapse and MRI disease activity on dimethyl fumarate, this patient would not be able to have natalizumab currently in the UK as she had 1 relapse, despite a relapse on treatment, potentially conferring a worse prognosis[27] • This patient would be eligible for anti-CD20 treatments (ofatumumab and ocrelizumab)[17] but her oncologist has advised against these in view of associations in clinical trials with higher rates of breast cancer[26] • The patient would only be eligible for natalizumab if she had a further relapse[17] • Waiting for a further relapse risks accumulation of permanent disability[27]
Expert group assessment: • The current NICE technology appraisal from 2007, which did not approve natalizumab for use in the 'suboptimal therapy group', is based on the old definition rather than the current natalizumab licensed indication:[2] ○ Patients with high disease activity despite treatment. This group is defined as patients who have failed to respond to a full and adequate course of a disease modifying therapy. Patients should have had at least one relapse in the previous year while on therapy[3] • Natalizumab could be considered alongside other highly effective therapies, with selection of treatment dependent on other clinical factors.	
Expert group recommendation: Natalizumab would be an option for patients who were escalating their treatment to a highly effective therapy after a relapse on their previous DMT. The risks and benefits of the treatments would be considered dependent on the other comorbidities of the person with MS, and the best therapy for the patient chosen.[1]	

4.4. Patients with low lymphocytes following previous DMT

Case study provided by Waqar Rashid, Consultant Neurologist, St Georges Hospital NHS Foundation Trust

Case study	**Current situation**
• 47 year old woman who works as a project manager • Diagnosed 4 years ago with a possible history not fully appreciated at the time dating back a further 3–4 years following her last completed pregnancy • She had two mild-moderate relapses (optic neuritis and sensory) in the 18 months prior to diagnosis with good recovery and commenced on dimethyl fumarate • Initially she was relapse-free and tolerated the medication over the next two years but from about 12 months developed lymphopenia with values ranging between 0.6–0.8 which persisted over the next 2 years but were stable • About 8 months ago she unfortunately sustained a spinal cord relapse resulting in increased urinary urgency and ongoing mobility problems • MRI showed 1 new cord and 1 new brain lesion • She was discussed by the MDT and it was agreed to escalate DMT • Based on one relapse with MRI activity she was offered escalation (highly active RRMS) with options as per algorithm being: ocrelizumab, ofatumumab, fingolimod and ponesimod [17] • She came off dimethyl fumarate six months ago in anticipation of escalation but her lymphocyte count has continued to be low at between 0.6–0.7 • There is concern as all her options to escalate will reduce lymphocyte count further and put her potentially at increased risk of infection;[28] she is extremely worried by this but also worried she is now off DMT and potentially at increased risk of relapse	• She does not meet RES criteria for natalizumab, so is currently not eligible for the therapy
Expert group assessment: • Natalizumab is the only high efficacy DMT that does not cause lymphopenia[28] but as this patient does not meet RES criteria she is currently not eligible for the therapy	
Expert group recommendation: Because of the relative preservation of immunity with natalizumab it is potentially the preferred option for this patient if it were available.[28] Natalizumab was the only high efficacy DMT used during the COVID-19 pandemic for this reason.[3]	

5. Literature review of real-world evidence studies

1. ***Association of Initial Disease-Modifying Therapy with Later Conversion to Secondary Progressive Multiple Sclerosis. Brown et al. (2019)[29]***

Aim: to determine the association between the use, the type of, and the timing of DMTs with the risk of conversion to secondary progressive MS.

Design: cohort study with prospective data from 68 neurology centres in 21 countries examining 1555 patients with RRMS.

Results: initial treatment with fingolimod, alemtuzumab or natalizumab was associated with a lower risk of conversion than initial treatment with glatiramer acetate or beta interferon (hazard ratio [HR], 0.66; p=0.046).

2. ***Clinical Outcomes of Escalation vs Early Intensive Disease-Modifying Therapy in Patients with Multiple Sclerosis. Harding et al. (2019)[30]***

Aim: to analyse long-term outcomes according to initial treatment strategy.

Design: population-based cohort study.

Results: 592 patients from South-East Wales (UK) were included. Individuals who received high-efficacy (HE) therapy as second-line (ESC) were most likely to receive natalizumab. Mean 5-year change in EDSS was lower in the early intensive treatment (EIT) group than the ESC group (0.3 vs. 1.2); this remained significant after adjustment for relevant covariates (p=0.002).

3. ***Initial high-efficacy disease-modifying therapy in multiple sclerosis: A nationwide cohort study. Due Buron et al. (2020)[31]***

Aim: to determine the effectiveness of HE DMT vs. medium-efficacy (ME) DMT as the first treatment choice in treatment-naive MS patients.

Design: cohort study. 194 patients starting HE DMT and 194 starting ME DMT.

Results: At 4 years follow-up, the probabilities of 6-month EDSS score worsening were 16.7% for HE DMT and 30.1% for ME DMT (p=0.006). Patients initiating HE DMT had a lower probability of relapse.

4. ***Timing of high-efficacy therapy for multiple sclerosis: a retrospective observational cohort study. He et al. (2020)[32]***

Aim: to compare long-term disability outcomes between patients who started HE DMT (rituximab, ocrelizumab, mitoxantrone, alemtuzumab, or natalizumab) within 2 years of disease onset with those who started 4-6 years after onset.

Design: retrospective international observational study using data from the MSBase and Swedish MS registries on RRMS patients.

Results: 277 (51%) of 544 patients started therapy early and 267 (49%) started late. The mean EDSS score was lower in the early start group throughout the 10-year follow-up , with a difference of -0.98 (p<0.0001).

5. ***Long-term disability trajectories in relapsing multiple sclerosis patients treated with early intensive or escalation treatment strategies. Iaffaldano et al. (2021)[33]***

Aim: to evaluate disability trajectories in RRMS patients treated with EIT or ESC.

Design: retrospective observational cohort study using prospective patient data from the Italian MS Register.

Results: 2702 RRMS patients were included. Mean annual delta-EDSS values were all significantly higher (p<0.02) in the ESC group compared to the EIT group.

6. ***Treatment Escalation vs Immediate Initiation of Highly Effective Treatment for Patients with Relapsing-Remitting Multiple Sclerosis. Spelman et al. (2021)[5]***

Aim: to investigate the association of national differences in DMT strategies for RRMS with disability outcomes.

Design: retrospective cohort study using data on 4861 patients from the Danish and Swedish national MS registries from the date of index DMT initiation until the last recorded visit.

Results: of 2700 Swedish patients who were included, 65.5% initiated a low to moderately effective DMT and 34.5% initiated a highly effective DMT. In contrast, 92-3% of total 1994 Danish patients initiated a low to moderately effective

DMT and 7.6% a highly effective DMT. The Swedish strategy was associated with a 29% reduction in rate of post-baseline confirmed disability worsening and a 24% reduction in the rate of reaching an EDSS score of 3.

Conclusion: Escalation of treatment efficacy was inferior to using more efficacious DMT as initial treatment.

7. ***Long-Term Efficacy Outcomes of Natalizumab vs. Fingolimod in Patients With Highly Active Relapsing-Remitting Multiple Sclerosis: Real-World Data From a Multiple Sclerosis Reference Center. Boziki et al (2021)[34]***

Aim: to report real-world experience of a MS Center with respect to natalizumab vs. fingolimod comparison in terms of efficacy and safety, referencing long-term follow-up.

Design: an analysis of retrospective data for all patients that received 2nd-line treatment with natalizumab (since May 2007) or fingolimod (since September 2011) and who either discontinued treatment or were currently under treatment (as of August 2020).

Results: of a total of 138 unmatched patients, 84 treated with natalizumab and 54 treated with fingolimod, 31 patients in each group were analysed following Propensity Score matching. Mean follow-up period for natalizumab- and fingolimod-treated patients was 4.43 ± 0.29 and 3.59 ± 0.32 years (p=0.057), respectively. In the matched analysis, time to disability improvement and time to disability worsening was comparable between groups. A higher proportion of patients remained free of relapse under natalizumab compared to fingolimod (p=0.021, HR: 0.25, 95% confidence interval [CI]: 0.08–0.8), as well as free of MRI activity (p=0.006, HR: 0.26, 95% CI: 0.08–0.6). Treatment discontinuation due to MRI activity was significantly higher for fingolimod-treated patients compared to natalizumab (p=0.019, HR: 0.12, 95% CI: 0.05–0.76).

8. ***Long Term Effectiveness of Natalizumab in Patients with Relapsing Remitting Multiple Sclerosis Treated in the Routine Care in Greece: Results from the Multicenter, Observational 5 Year Prospective Study 'TOPICS Greece. Dardiotis et al. (2021)[35]***

Aim: to provide long-term data on the safety and effectiveness of natalizumab in patients with RRMS treated in a routine care setting in Greece

Design: a multicenter, single-country, prospective 5-year observational study

Results: Between 19-Apr-2012 and 18-Dec-2014, 304 eligible adults were enrolled in the study by 20 hospital-based neurologists. The 1-year ARR before treatment initiation was 1.859, while the ARR during the first year of treatment was 0.131, representing a significant 93% reduction (p<0.001). The ARR over the median treatment period of 59.4 months was 0.109. Patients with ≤1 relapse in the pre-natalizumab year (46.1%) and those having received ≤1 prior disease-modifying therapy (57.9%) displayed significantly lower on-natalizumab ARR. The 1-, 2-, 3-, 4- and 5-year cumulative probabilities of EDSS progression were 3.2, 6.2, 9.7, 13.4, and 17.4%, respectively; the respective probabilities of EDSS disability improvement were 18.3, 25.1, 27.4, 28.0, and 30.1%. Over a median safety data collection period of 48.7 months, 4.6% of the patients experienced ≥ 1 serious adverse event, with infections (reported in 1.0%) being the most common.

9. ***Initial treatment strategy and clinical outcomes in Finnish MS patients: a propensity-matched study. Hänninen et al. (2022)[36]***

Aim: to compare outcomes of initial treatment with infusion therapies and ME DMT.

Design: propensity-matched cohort of Finnish RRMS patients.

Results: 154 patients initiated with HE DMT (natalizumab, alemtuzumab, ocrelizumab or rituximab) and 1771 initiated with ME DMT. Probability of 6-month CDP at 5 years was 28.4%.in the HE DMT patients and 47% in the ME DMT patients (p=0.013). Probability of relapse was 34.6% and 47.2% for the HE DMT and ME DMT patients, respectively (p=0.019).

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NICE National Institute for Health and Care Excellence

Multiple Technology Appraisal

Natalizumab and Tyruko (natalizumab biosimilar) for treating highly active relapsing-remitting multiple sclerosis after at least one disease modifying therapy [ID6269]

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology(ies) and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1.Your name	[redacted]
2. Name of organisation	MS Society
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	The MS Society is the UK's largest charity for people with MS. We fund world-leading research, provide information and support, and campaign for the rights of people affected by MS. Our ultimate goal is to find a cure. Until then, we're working to make sure no one has to face MS alone. In 2023, our helpline and information services responded to over 25,000 enquiries and 4 million people visited our website. Our network of 230 groups supports the MS community at a local level, across the UK. We are a registered charity, with the vast majority of our income coming from individual and philanthropic donations and legacies. We are not a member organisation.
4b. Has the organisation received any funding from the company(ies) bringing the treatment(s) to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company,**	Merck Serono • May 2024 - Grant towards helpline specialist nurses service - £20,000 Roche • Feb 2024 - Sponsorship of MS Frontiers conference - £10,000 • May 2024 - Grant towards the MS helpline - £35,000 Sanofi Genzyme • June 2024 - sponsorship of MS Frontiers conference - £10,000

amount, and purpose of funding.	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	We speak daily to people about their experiences with, or supporting someone with, multiple sclerosis. For years we've worked alongside people with MS and their carers to understand what's important to them. For this submission, we drew on the experiences of those who have used the related disease modifying therapy (DMT) natalizumab, our 2022 "My MS My Needs" survey of the experiences of people with MS in the UK (1), our 2022 "Friends and Family" survey (2) of loved ones of people with MS in the UK, and on the results of an MS Society funded project that aimed to understand DMT treatment decisions from the perspective of people with relapsing remitting MS (3). 1. MS Society (2023) My MS My Needs 2022 2. MS Society (2023) Findings from the 2022 Family & Friends Survey 3. Manzano, A. et al. (2019) CRIMSON - Considering Risk and benefits In Multiple Sclerosis treatment selection: Final Report

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	More than 150,000 people in the UK live with MS, and over 7,000 people are diagnosed each year. This means around 1 in every 400 people in the UK has MS. In the UK people are mostly commonly diagnosed in their twenties, thirties, and forties, although the first signs of MS can start years earlier. Around three quarters of people with MS are women. MS can be relentless, painful and exhausting. It can make it harder to do everyday things like walk, talk, eat and think. Symptoms can fluctuate, making life unpredictable. They can include loss of balance, stiffness, spasms, speech problems, fatigue, pain, bladder and bowel issues, and vision problems. Many symptoms are 'invisible' which can make it difficult for others to understand the impact MS has on somebody. Living with a chronic, disabling and degenerative condition such as MS is hard. It is also expensive. There are often substantial extra costs, such as accessible transport, specialist equipment, medication and help with household activities. People with MS have reported funding 75% of non-medical costs themselves, with costs increasing as disability progresses (4). Around 85% of people with MS are first diagnosed with relapsing remitting MS. A relapse is defined as an episode of neurological symptoms which lasts for at least 24 hours and occurs at least 30 days after the onset of any previous episode. Symptoms may last from weeks to months and relapses can vary from mild to severe. Some acute relapses may require hospital treatment, whilst many relapses are managed at home with the support of healthcare professionals. People with MS can experience a wide range of distressing and debilitating symptoms during a relapse. In addition, evidence shows that disability doesn't get worse between relapses but after each relapse it can end up worse than before. These are important reasons to reduce the frequency and severity of relapses by making sure that people have access to the best treatment for them, as soon as possible. Relapses can have a significant emotional impact on a person. The loss of independence that can often come with a relapse mean that people can often feel a burden on their family. Relapses are often unpredictable and distressing, leaving people feeling frustrated, anxious and causing disruption to everyday life.

	Most people with relapsing remitting MS will eventually go on to develop secondary progressive MS. Progressive forms of MS are characterised by a sustained accumulation of disability independent of relapses. People with MS live with great uncertainty, not knowing from one day to the next whether they will be able to move, to see or to live even a remotely 'normal' life. As each person's response to DMTs is different, more effective options available on the NHS will result in more people finding a treatment which best suits them. **Impact on carers** The progressive, fluctuating and unpredictable nature of MS presents particular challenges to families and carers. It can make balancing work, education and taking care of one's own health and wellbeing difficult. Our 2022 My MS My Needs survey found that 38% of people living with MS hadn't received the care and support they needed to assist with daily living in the prior year (1). Much of the care and support people need falls to their loved ones. Over 6 in 10 respondents received one or more hours of unpaid care from friends and/or family each week. Of these, over half received 20 hours or more. The most common areas of support needed included; shopping, cleaning, and laundry, cooking meals, housework and gardening, getting out the house and washing and bathing. 542 people completed our Family and Friends survey in 2022 (2). The majority said that they had made moderate or major adjustments to their lives because of their loved one's MS. Two thirds said that they experienced feelings of stress or worry because of the impact of MS. Other common experiences included anxiety, tiredness and disturbed or lost sleep. We know that the complexity of care and support needs increases with age, as the disease progresses. Treatments that slow the progression of disability therefore not only benefit the person with MS, but impact on their carer too. 4. Nicholas, R. et al. (2020) Personal and societal costs of multiple sclerosis in the UK: A population-based MS Registry study

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	People with MS need timely access to many different healthcare services across primary, secondary, tertiary and community care, to live as fully and independently as possible. These include: neurology; MS nursing; neurorehabilitation; pain and spasticity management; emotional and psychological support; continence support; as well as everyday primary care. However, our 2022 My MS My Needs survey of over 6,500 people showed too many people with MS are unable to access the treatment, care and support they need (1). There is significant variation in the quality and availability of care across England. Our survey found that: • There was national variation in the proportion of people with relapsing remitting MS on a disease modifying therapy. Of respondents with relapsing remitting MS in England, 56% were on a DMT compared to 73% in Northern Ireland. • People who weren't on DMTs were less likely to have seen an MS specialist in the previous 12 months. • Over a third (35%) reported not having received enough information from healthcare professionals about drugs available to support the treatment of their MS. • One in five (20%) respondents who needed to have an appointment with a neurologist, did not get one in the previous 12 months. • People reported unmet need across continence care, cognitive support, emotional support, physiotherapy and support to be active. In all areas, there was greater unmet need than in 2019. From our everyday contact with people with MS and healthcare professionals working with them, we know that people are waiting a long time to see a neurologist, which causes delays in receiving a diagnosis and starting treatment. Furthermore, it can take a long time for a DMT to be available everywhere after it has been recommended for use, despite the statutory obligations of the NHS. This causes huge frustration for patients affected. We often hear how services aren't joined up and that people with MS must explain their condition or changes in their MS repeatedly to different clinicians.

8. Is there an unmet need for patients with this condition?	Many unmet needs have been covered in the response to question 7. With regards to treatment options, over a dozen DMTs are now available on the NHS to people with relapsing remitting MS. However, we know that there are some areas where not every DMT is available to everyone eligible due to commissioning barriers and/or lack of resource and workforce capacity. Every person in England should have access to the full range of DMTs recommended by NICE, in line with the statutory obligations of the NHS. People with MS can face difficult choices when they come to consider the risks and benefits of the different DMTs. These decisions are determined by a variety of factors including eligibility, efficacy, risks, possible side effects, the method, location and frequency of administration, and lifestyle factors (3). Choosing a DMT is a highly personal decision. The more effective treatments that are available, the greater the choice for patients. Side effects can have a considerable effect on quality of life, meaning individual patients may be unable to tolerate them. Considering that many people with relapsing MS may need to switch to an alternative DMT during the course of their disease, there remains a need for novel, effective DMTs with a good side effect and safety profile for relapsing MS. One person with MS we spoke to, Donna (pseudonym) emphasised the importance of day-to-day side effects in choice and compliance in DMT use, saying that "*it's a very important part of decision-making on whether you are prepared to take the medicine in the first place as well as being able to cope with medicine in the longer term".* She said that she had made the decision not to commence some DMTs due to her concern over safety profiles, and had switched DMT several times due to side effects which "*impacted my home life, my work life and my ability to get on with my day".* She went on to say that *"medicines with a more tolerable side effect profile are very very important. Medicine side effects impact the choice of medicine people will take, meaning some really effective medicines won't be taken, for a good reason".* It is *"essential there is a suite of medicine as people react to the medicines differently, both in whether they think the risk/benefit is appropriate for them and if they can tolerate the side effects as well as how well the medicines work for them at that time in their MS journey…it's very easy to dismiss improvement in side effect profile if it's not you actually with the choice on which to use or actually having to tolerate the side effects"* Treatment options that do not require clinic or hospital appointments to administer them have an obvious advantage, potentially reducing pressure on NHS services and causing less disruption to a patient's life. For

	DMTs like natalizumab that can be administered in different ways, it is important that eligible patients have access to the different options.

Advantages of the technology(ies)

9. What do patients or carers think are the advantages of the technology(ies)?	When it comes to making decisions on DMTs, outcomes important to people with MS include a reduction in relapse rate, the slowing of disability progression, and a reduction in evidence of active disease. Natalizumab is a highly effective DMT that for some means being able to live a relatively 'normal' life. An MS Society funded project that aimed to understand DMT treatment decisions of people with relapsing remitting MS, indicated that mode of delivery plays a role in decisions on whether to take or to delay starting a DMT (3). It is important that eligible patients have access to all available treatment formats including subcutaneous and intravenous options. For some people on Tysabri, the option to move to subcutaneous injection from IV infusion has been positive. Others prefer IV.

Disadvantages of the technology(ies)

10. What do patients or carers think are the disadvantages of the technology(ies)?	Being on natalizumab increases the chance of developing progressive multifocal leukoencephalopathy (PML). This is a key factor in patients' and clinicians' consideration of natalizumab as a treatment option.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology(ies) than others? If so, please describe them and explain why.	People with highly active relapsing MS who are considering pregnancy would benefit from having access natalizumab. It is a highly effective DMT with fewer restrictions on family planning compared to some other DMTs. Subcutaneous Tysabri may be delivered at home if six doses have been administered in hospital without problems. This may benefit people who find it harder to attend hospital appointments whether that's due to distance, cost, mobility, caring responsibilities, work commitments, precarity of work and shift patterns for those on lower-incomes, or sensitivity to the highly stimulating hospital environment.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology(ies)?	MS affects around three times as many women as men. Any NICE recommendation that resulted in fewer available treatment options for the wider population of people with highly active relapsing MS is likely to have a disproportionate impact on women. A decision by NICE not to recommend natalizumab for the wider population of people with highly active relapsing MS may have a disproportionate impact on younger people, and particularly women, who are more likely to consider family planning in their treatment decisions. Natalizumab offers fewer restrictions on family planning compared to some other DMTs.

Other issues

13. Are there any other issues that you would like the committee to consider?	We are aware that the JCV antibody tests used with Tysabri and biosimilar, Tyruko, appear to have differing sensitivity. It is vital that patients can understand their risk of PML so that they can make informed decisions about their treatment.
14. What factors would influence treatment choices for multiple sclerosis for you, or the person you care for? Would these include: • **Route and duration of administration?** • **Perceived effectiveness of the drug?** • **Potential side effects?**	This is included earlier in the submission.

Key messages

24. In up to 5 bullet points, please summarise the key messages of your submission.	• Relapsing remitting MS is unpredictable. Relapses can cause painful, debilitating symptoms and emotional distress, causing disruption to someone's life and lead to increased disability after each relapse. • Choosing a DMT is determined by a variety of factors including eligibility, efficacy, side effects, risks, the method, location and frequency of administration, and lifestyle factors. As each person's response to DMTs is different, offering a wider range of more effective options to people with highly active relapsing remitting MS will result in more people finding a treatment which best suits them, preventing irreversible disability. • Natalizumab is a highly effective DMT. It is available as a subcutaneous injection or intravenous infusion, which can increase patient choice. Natalizumab offers fewer restrictions on family planning than other DMTs. • It is vital that patients can understand the result of JCV tests and risk of PML so that they can make informed decisions about their treatment.

Thank you for your time.

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Multiple Technology Appraisal

Natalizumab and Tyruko (natalizumab biosimilar) for treating highly active relapsing-remitting multiple sclerosis after at least one disease modifying therapy [ID6369]

Professional organisation submission

Thank you for agreeing to give us your organisation's views on the technology(ies) and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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About you

NICE National Institute for Health and Care Excellence

1. Your name	[redacted]
2. Name of organisation	Association of British Neurologists
3. Job title or position	[redacted]
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes A specialist in the treatment of people with this condition? Yes A specialist in the clinical evidence base for this condition or technology? Yes Other (please specify):
5a. Brief description of the organisation (including who funds it).	The Association of British Neurologists' is a professional membership organisation and its mission is to improve the health and well-being of people with neurological disorders by advancing the knowledge and practice of neurology in the British Isles. The ABN receives funding mainly from its member subscriptions and annual conference income. Additional funding from external charity organisations is received to solely fund fellowships. Additionally, the ABN receives sponsorship from pharmaceutical companies. Sponsoring companies have no input, control nor opportunity to influence the ABN.

5b. Has the organisation received any funding from the manufacturer(s) of the technology(ies) and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	In the past 12 months, the ABN has received sponsorship from the following companies to support the ABN Annual Conference. Sponsorship companies have no editorial input, control over the agenda, speaker selection, content development nor opportunity to influence the conference. Sponsorship is £18,020 per company. • Abbvie • Alnylam • Angelini • argenx • Biogen • Eisai • Eli Lilly • Janssen • Pfizer • Roche • Sanofi • Teva • UCB
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	The remit of this MTA is to appraise the clinical and cost effectiveness of natalizumab (Tysabri) and natalizumab biosimilar (Tyruko) within its marketing authorisation for treating highly active relapsing-remitting multiple sclerosis after at least one disease modifying therapy. The main aim of treatment in this context is to prevent further clinical relapses and inflammatory activity (i.e. a reduction in relapse rate in those who have failed on initial therapy), thus preventing longer term progression and worsening disability.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	A clinically significant treatment response would be suppression of clinical relapses and inflammatory MRI activity. Whilst the goal of treatment is to reduce as much as possible, a clinically significant response would be reduction of relapse rate to less than baseline (pre-treatment or on first line treatment).
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	There is an unmet need in terms of highly effective therapies for those who have failed first line treatment (i.e. show continuing relapses on treatment meeting the criteria of highly active MS), particularly those who have either had highly effective treatment as a first line, and/or those who are planning pregnancy. At present, natalizumab is not commissioned for this indication, instead patients have to wait for a second, potentially disabling relapse in order to meet criteria for escalation to this therapy. Where patients have failed antiCD20 therapy as first line (currently the most commonly prescribed DMT in England according to NHSE data), they are unable to access any potentially pregnancy compatible DMT without waiting for a second relapse or accepting an induction therapy with a potential 2 year delay to trying to conceive (not an issue for those not planning families) – a clear equalities issue. Additionally, natalizumab is one of the few DMT with no peripheral immunosuppressive effects, offering a unique mode of action. This is relevant to those people with MS who may not want either long term immunosuppression or induction therapies, meaning that we can offer a broader range of treatment options without needing to wait for avoidable relapses and preventable disability.

What is the expected place of the technology(ies) in current practice?

9. How is the condition currently treated in the NHS?	NHSE commissioning criteria guide clinical practice; these are based on NICE TAs. These clearly detail which therapies can be used first and second line, and when. At present, natalizumab is an outlier, as it is the only therapy where rapidly evolving severe (RES) MS is required to escalate (for all other DMT used second line, highly active MS on treatment is sufficient)
9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	https://www.england.nhs.uk/wp-content/uploads/2024/03/treatment-algorithm-for-multiple-sclerosis-disease-modifying-therapies-july-23.pdf
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Whilst the pathway is well defined, and MDT meetings ensure that differences in individual clinical practice are evened out to some degree there remain challenges. A major challenge for all MS clinicians prescribing DMTs is around the variable eligibility requirements. Due to differences in clinical trial eligibility and the ways in which these have been applied within TAs, the resulting NHSE DMT prescribing algorithm is overly complex, and does not reflect the practical uses of these treatments internationally. There is an urgent need to rationalise this in order to ensure that patients are able to access the most suitable DMT for them in a timely manner. This has been highlighted in the recent ABN DMT guidelines. An important first step towards this would be the rationalisation of second line escalation treatment, so that the criteria for obtaining each treatment is aligned, rather than forcing patients who wish to access natalizumab to wait for a second, potentially disabling relapse.
9c. What impact would the technology(ies) have on the current pathway of care?	It would help to rationalise the current pathway of care, improving efficiency within the MDT. It would also offer more equitable access to highly effective treatments for those who are planning pregnancy, which has not been properly considered in previous iterations of this pathway.
10. Will the technology(ies) be used (or is it already used) in the same way as	Yes, although this MTA would expand potential access for those who have relapses on first line treatment (i.e. those with treatment failure).

current care in NHS clinical practice?	
10a. How does healthcare resource use differ between the technology(ies) and current care?	This MTA would extend the use of natalizumab to those with highly active MS on treatment, whereas currently it can be used only in those with rapidly evolving severe MS on treatment. The difference is that RES MS requires two relapses within a year on treatment with MRI change, whereas highly active MS on treatment requires only one relapse.
10b. In what clinical setting should the tech technology(ies) nology be used? (For example, primary or secondary care, specialist clinics.)	Specialist clinics as currently prescribed for all other disease modifying treatments with MDT approval
10c. What investment is needed to introduce the technology(ies)? (For example, for facilities, equipment, or training.)	None
11. Do you expect the technology(ies) to provide clinically meaningful benefits compared with current care?	Yes – if approved, this MTA would make natalizumab available to those who have highly active MS despite an adequate course of treatment, rather than mandating waiting for these patients wait to have a second, potentially avoidable relapse. We anticipate that this meaningful benefit (fewer relapses) would lead to less disability for these patients in the longer term. This option would be of particular relevance to those patients for whom other treatments are not suitable, particularly those who are planning pregnancy in the near future. There is currently inequity, in that many of the treatments suitable for patients with highly active MS whilst on therapy are either incompatible with pregnancy (demonstrated to be teratogenic, or presumed so due to class effect), or require a full course of induction therapy, potentially mandating delaying of pregnancy for 18 months. Extending the availability of natalizumab, a DMT with a proven safety profile in pregnancy, to these patients would have meaningful clinical benefit compared to forcing them to wait for a second relapse in order to be able to access treatment escalation options.
11a. Do you expect the technology(ies) to increase	No

length of life more than current care?	
11b. Do you expect the technology(ies) to increase health-related quality of life more than current care?	Yes – by removing the need for people escalating to natalizumab to have a second relapse (thus meeting the criteria for RES MS), and instead enabling earlier escalation we would anticipate that the quality of life of this cohort of people with MS would improve both in the short and longer term. Further, this change would align natalizumab with other DMTs that are used in those with ongoing disease activity on first line treatment, rationalising the decision making process and reducing stress associated with this for people with MS.
12. Are there any groups of people for whom the technology(ies) would be more or less effective (or appropriate) than the general population?	None identified within this population

The use of the technology(ies)

13. Will the technology(ies) be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	If approved, this MTA would simplify things for healthcare professionals across the MDT along with the patients they care for. At present, in the cohort of patients who have highly active MS despite adequate treatment with DMT, the criteria for escalation to different therapies is different. Aligning the criteria for escalation to natalizumab to that applied to other therapies will rationalise and simplify MDT team working. It will also make things easier for patients when weighing up different treatments to have all escalation therapies on an equal footing.

14. Will any rules (informal or formal) be used to start or stop treatment with the technology(ies)? Do these include any additional testing?	Safety monitoring – including JCV testing – will guide treatment duration and switching. This is already well established where natalizumab is used for the treatment of RES-MS. We do not anticipate that the approach to this would be any different with a slight change to the MTA.
15. Do you consider that the use of the technology(ies) will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	The equalities impact is potentially substantial. We had been working with NHSE to extend the scope of use of natalizumab in those with highly active MS not meeting RES criteria for the purposes of pregnancy planning via a priority workstream within the PPP pathway. However, this MTA has paused this work. At present, there are a cohort of people with MS who are denied access to highly active therapy with proven safety data in pregnancy (those who have highly active MS whilst on antiCD20 therapy) – all other escalation options need to be stopped prior to conception, or are induction therapies mandating a full course with wash out, thus delaying pregnancy plans. Widening access to natalizumab will have benefits related to improved MS care in and around pregnancy that will not be included in the QALY calculations.
16. Do you consider the technology(ies) to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve	Only in the ways described above.

the way that current need is met?	
16a. Is the technology(ies) a 'step-change' in the management of the condition?	No – this is an extension of the existing use of this product.
16b. Does the use of the technology(ies) address any particular unmet need of the patient population?	Yes – there is a clear unmet need from an equalities perspective. This is outlined in the answer to question 15.
17. How do any side effects or adverse effects of the technology(ies) affect the management of the condition and the patient's quality of life?	The main adverse effect associated with natalizumab is the risk of JCV-associated PML. This is adequately addressed by a risk mitigation protocol, with regular serological testing, MRI monitoring and treatment paradigms for if this is detected at the earliest stages. Whilst PML can adversely affect quality of life, with current risk mitigation approaches this risk is managed well with clear systems and lines of responsibility.

Sources of evidence

18. Do the clinical trials on the technology(ies) reflect current UK clinical practice?	The clinical trials of natalizumab were not restricted to the RES-MS population. Current usage as directed by commissioning criteria is therefore more restricted than in the clinical trials. This change would bring the use of natalizumab more into line with that seen in trials.
18a. If not, how could the results be extrapolated to the UK setting?	N/A

18b. What, in your view, are the most important outcomes, and were they measured in the trials?	Most important outcomes are relapses (relapse rate), inflammatory MRI activity and longer term disability outcomes. These were all captured within trials.
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	N/A
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	The risk of PML was seen in the original trials – indeed these were temporarily suspended. However, in the decades of experience with natalizumab, highly effective risk mitigation strategies have been put in place. No additional adverse events of widespread clinical significance have come to light.
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance TA794?	TA794 is for diroximel fumarate and dates to 2022. A number of NICE TAs have been updated since this time in light of new evidence.
21. How do data on real-world experience compare with the trial data?	Real world data support the clinical trial data, demonstrating the utility of natalizumab when used for those with ongoing disease activity on first line treatment.

Equality

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	There are substantial equality reasons supporting this MTA. We had been working with NHSE to extend the scope of use of natalizumab in those with highly active MS not meeting RES criteria for the purposes of pregnancy planning via a priority workstream within the PPP pathway. However, this MTA has paused this work. At present, there are a cohort of people with MS who are denied access to highly active therapy with proven safety data in pregnancy (those who have highly active MS whilst on antiCD20 therapy) – all other escalation options need to be stopped prior to conception, or are induction therapies mandating a full course with wash out, thus delaying pregnancy plans. Widening access to natalizumab will have benefits related to improved MS care in and around pregnancy that will not be included in the QALY calculations.
22b. Consider whether these issues are different from issues with current care and why.	These issues specifically relate to the differential positioning of natalizumab as a second line/escalation therapy compared to all other second line treatment options. There is no trial based rationale for this difference. This reflects a specific equalities issue for this cohort of patients.

Topic-specific questions

23. What factors influence treatment sequencing after disease progression on the first disease modifying therapy?	Factors include: the initial therapy used, initial MS disease activity, MS disease activity at the time of escalation, patient preference, pregnancy and family plans,
24. Who would be treated with autologous haematopoietic stem cell transplantation in clinical practice?	In practice – whilst those with disease activity on first line treatment would be eligible for HSCT, only a minority of patients are keen to consider this. For some patients, this may not relate to the degree of disease activity. It is more common that patients consider this treatment having failed >1 MS DMT. Those considering future pregnancies will usually not consider this treatment given the effects on fertility.
25. Natalizumab is available in a subcutaneous and intravenous formulation. What would determine use of each formulation in clinical practice?	Local practice is the largest driver of formulation use. This primarily results from pressures around infusion capacity. Additionally, patient preference and ease of venepuncture may influence decisions. AS homecare for sc administration is not supported, this is not being used as a mode of delivery in practice, meaning that patients still need to attend for sc administration.
26. How is highly active relapsing remitting multiple sclerosis defined in clinical practice?	The definition is as per https://www.england.nhs.uk/wp-content/uploads/2024/03/treatment-algorithm-for-multiple-sclerosis-disease-modifying-therapies-july-23.pdf Patients with an unchanged or increased relapse rate or ongoing severe relapses compared with the previous year despite treatment with beta interferon. [From NICE TA254): Fingolimod for the treatment of highly active relapsing- remitting multiple sclerosis] The NICE TA on cladribine offers a different definition: “defined as 1 relapse in the previous year and magnetic resonance imaging (MRI) evidence of disease activity.”

27. Would you expect the natural progression of multiple sclerosis and response to disease modifying therapies, including natalizumab, to differ in people with highly active relapsing remitting multiple sclerosis compared with other forms of multiple sclerosis?	I would expect this cohort of people to have a similar disease course to those with RES MS, and to those with RRMS and disease activity on first line therapy.

Key messages

24. In up to 5 bullet points, please summarise the key messages of your submission.	• • • • •

Thank you for your time.

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sSingle Technology Appraisal

Natalizumab and Tyruko (natalizumab biosimilar) for treating highly active relapsing-remitting multiple sclerosis after at least one disease modifying therapy [ID6369]

Clinical expert statement

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

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Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

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Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals (section 3.2) for more information.

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Part 1: Treating highly active relapsing-remitting multiple sclerosis and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Professor Ruth Dobson
2. Name of organisation	Queen Mary University London/Barts Health NHS Trust
3. Job title or position	Professor of Clinical Neurology
4. Are you (please tick all that apply)	☒ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with highly active relapsing-remitting multiple sclerosis? ☒ A specialist in the clinical evidence base for highly active relapsing-remitting multiple sclerosis or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	I have no links to the tobacco industry

8. What is the main aim of treatment for highly active relapsing-remitting multiple sclerosis? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	The primary aim of treatment for highly active relapsing remitting multiple sclerosis (RRMS) is to prevent further clinical relapses and inflammatory activity (on MRI), as measured in clinical practice by a reduction in relapse rate/reduced number of relapses and/or reduced new or active disease on MRI. Failure to supress relapses and inflammatory disease activity early in the MS disease course has been associated with the risk of longer-term progression and disability in multiple large real-world cohorts; thus reducing these short term metrics links in to an aim to reduce the risk of (and potentially prevent) longer term progression and disability.
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount) • When is treatment response assessed following initiation of a new therapy? • Would all people whose condition does not meet response criteria switch treatments? • If yes, what factors impact the choice of subsequent treatments? • Would people stop treatment for reasons other than a lack of response?	A clinically significant treatment response would be reduction and/or suppression of clinical relapses and inflammatory MRI activity. Whilst the goal of treatment is to reduce this inflammatory disease activity as much as possible, a clinically significant response would be reduction of relapse rates to less than pre-treatment baseline (either compared to prior to any treatment or compared to first line treatment where breakthrough disease activity has occurred).
10. In your view, is there an unmet need for patients and healthcare professionals in highly active relapsing-remitting multiple sclerosis?	There is an unmet need in terms of highly effective therapies for those who have failed first line treatment (i.e. show continuing relapses on treatment meeting the criteria of highly active MS), those who have failed highly effective treatment as a first line, and/or those who are planning pregnancy. An important unmet need is equitable access to treatment for women planning pregnancy – women are

	commonly de-escalated or denied access to highly effective treatments because of their pregnancy plans, potentially leading to longer term avoidable disability. Natalizumab has a well-established safety profile in pregnancy and breastfeeding, and offers excellent control of MS disease activity. Expanding the scope of patients who can access this treatment would be an important step forward in terms of ensuring equity of access to effective treatments for people with protected characteristics. There is also a need for non-immunosuppressive highly active treatment – at present, if patients with highly active disease not meeting RES criteria want to start on or escalate to a highly effective treatment, they only have access to immunosuppressive therapies; concerns regarding cumulative risks associated with these therapies are increasing amongst both clinicians and patients. It is important to note that they have previously been concerns regarding cumulative risk of adverse events associated with natalizumab therapy. Effective risk mitigation in terms of monitoring is in place, with identification and treatment switching for those at highest risk of adverse events on therapy. Such risk mitigation strategies are not available for other treatments which have emerging evidence of cumulative risks of adverse events. At present, natalizumab is not commissioned either first or second line for highly active RRMS, instead patients have to wait for a second, potentially disabling relapse in order to meet RES criteria for escalation to this therapy. Where patients have failed antiCD20 therapy as first line (currently the most commonly prescribed DMT in England according to NHSE data), they are unable to access any potentially pregnancy compatible DMT without waiting for a second relapse or accepting an induction therapy with a potential 2 year delay to trying to conceive (not an issue for those not planning families) – this is an equalities

	issue affecting the overall treatment landscape that has not been considered with sequential TAs. Natalizumab is one of the few highly effective treatments for RRMS which has no peripheral immunosuppressive effects, offering a unique mode of action. This is relevant to those people with MS who may not want either long-term immunosuppression or induction therapies, meaning that we can offer a broader range of treatment options without needing to wait for avoidable relapses and preventable disability.
11. How is highly active relapsing-remitting multiple sclerosis currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	NHSE commissioning criteria guide clinical practice; these are based on NICE TAs. These are contained within the following hyperlink: https://www.england.nhs.uk/wp-content/uploads/2024/03/treatment-algorithm-for-multiple-sclerosis-disease-modifying-therapies-july-23.pdf These clearly detail which therapies can be used first and second line, and when. At present, natalizumab is an outlier, as it is the only therapy where rapidly evolving severe (RES) MS is required to escalate (for all other DMT used second line, highly active MS on treatment is sufficient). Whilst the pathway is well defined, and MDT meetings ensure that differences in individual clinical practice are evened out to some degree there remain challenges. A major challenge for all MS clinicians prescribing DMTs is around the variable eligibility requirements. Due to differences in clinical trial eligibility and the ways in which these have been applied within TAs, the resulting NHSE DMT prescribing algorithm is overly complex, and does not reflect the practical uses of these treatments internationally. There is an urgent need to rationalise this in order to ensure that patients are able to access the most suitable DMT for them in a timely manner. This has been highlighted in the recent ABN DMT guidelines

	(currently in press). An important first step towards this would be the rationalisation of second line escalation treatment, so that the criteria for obtaining each treatment is aligned, rather than forcing patients who wish to access natalizumab to wait for a second, potentially disabling relapse. This TA would be an important step forward to rationalise the current pathway of care, improving efficiency within the MDT. It would also offer more equitable access to highly effective treatments for those who are planning pregnancy, which has not been properly considered in previous iterations of this pathway.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	Yes, although this MTA would expand potential access to a wider group of those who have relapses on first line treatment (i.e. those with treatment failure). It would extend the use of natalizumab to those with highly active MS on treatment (can be defined after one breakthrough relapse), whereas currently it can be used only in those with rapidly evolving severe MS (requires 2 relapses) on treatment. RES MS requires two relapses within a year on treatment with MRI change, whereas highly active MS on treatment requires only one relapse. This would mean that people could access the drug earlier – without the need to wait for a second, potentially disabling relapse – with no difference to current care in terms of drug delivery and monitoring. Importantly, this approach was used during the initial stages of the COVID pandemic due to concerns regarding immunosuppressive DMTs (antiCD20s). This did not lead to destabilisation of services, and the slight extension in access was clinically welcomed and used appropriately. Importantly, it offered patients improved chose with access to highly effective non-immunosuppressive medication.

13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	Yes – if approved, this MTA would make natalizumab available to those who have highly active MS despite an adequate course of treatment, rather than mandating waiting for these patients wait to have a second, potentially avoidable relapse. We anticipate that this meaningful benefit (fewer relapses) would lead to less disability for these patients in the longer term. This option would be of particular relevance to those patients for whom other treatments are not suitable, particularly those who are planning pregnancy in the near future. There is currently inequity, in that many of the treatments suitable for patients with highly active MS whilst on therapy are either incompatible with pregnancy (demonstrated to be teratogenic, or presumed so due to class effect), or require a full course of induction therapy, potentially mandating delaying of pregnancy for 18 months. Extending the availability of natalizumab, a DMT with a proven safety profile in pregnancy, to these patients would have meaningful clinical benefit compared to forcing them to wait for a second relapse in order to be able to access treatment escalation options. By removing the need for people escalating to natalizumab to have a second relapse (thus meeting the criteria for RES MS), and instead enabling earlier escalation we would anticipate that the quality of life of this cohort of people with MS would improve both in the short and longer term. Further, this change would align natalizumab with other DMTs that are used in those with ongoing disease activity on first line treatment, rationalising the decision making process and reducing stress associated with this for people with MS.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	No

15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	If approved, this MTA would simplify things for healthcare professionals across the MDT along with the patients they care for. At present, in the cohort of patients who have highly active MS despite adequate treatment with DMT, the criteria for escalation to different therapies is different. Aligning the criteria for escalation to natalizumab to that applied to other therapies will rationalise and simplify MDT team working. It will also make things easier for patients when weighing up different treatments to have all escalation therapies on an equal footing.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Safety monitoring – including JCV testing – will guide treatment duration and switching. This is already well established where natalizumab is used for the treatment of RES-MS. We do not anticipate that the approach to this would be any different with a slight change to the MTA.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	The equalities impact is substantial and supports this TA. We had been working with NHSE to extend the scope of use of natalizumab in those with highly active MS not meeting RES criteria for the purposes of pregnancy planning via a priority workstream within the PPP pathway. However, this MTA has paused this work, and so the equalities issues identified by the clinical community remain unaddressed. At present, there are a cohort of people with MS who are denied access to highly active therapy with proven safety data in pregnancy (those who have highly active MS whilst on antiCD20 therapy) – all other escalation options need to be stopped prior to conception, or are induction therapies mandating a full course with wash out, thus delaying pregnancy plans. Widening access to natalizumab will have benefits related to improved MS care in and around pregnancy that will not be included in the QALY calculations.

	Our recent research (submitted for publication) has examined the cost effectiveness of continuing natalizumab for pregnancy vs costs of stopping treatment in terms of total NHS costs associated with relapses. We have shown that the cost of stopping treatment is higher than continuing when drug costs (list price prior to the introduction of generic medication) are weighed up against the costs associated with relapse, and the risk of relapse is taken into account. This These data have not yet been published and so will not have been taken into account.
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	Only in the ways described above – this change (which would probably be described as an extension rather than a step change) would provide earlier access to highly effective therapy and provide a step change in equitable access to treatments.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The risk of treatment associated PML is the only adverse event associated with therapy that would affect QoL. However, we now have decades of experience of risk minimisation strategies for this, including effective patient selection, risk stratification, extended dose intervals, graded monitoring according to risk band, and de-escalation to other therapies for those judged to be at unacceptably high cumulative risk. Thus whilst PML can adversely affect quality of life, with current risk mitigation approaches this risk is managed well with clear systems and lines of responsibility.
20. Do the clinical trials on the technology reflect current UK clinical practice?	The clinical trials of natalizumab were not restricted to the RES-MS population. Current usage as directed by commissioning criteria is therefore more restricted

• If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	than in the clinical trials. This change would bring the use of natalizumab more into line with that seen in trials. The most important outcomes are relapses (relapse rate), inflammatory MRI activity and longer term disability outcomes. These were all captured within trials. The risk of PML was seen in the original trials – indeed these were temporarily suspended. However, in the decades of experience with natalizumab, highly effective risk mitigation strategies have been put in place. No additional adverse events of widespread clinical significance have come to light.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance TA767, 706, 699, 616, 553, 312, 254 and 127?	TA794 is for diroximel fumarate and dates to 2022. A number of NICE TAs have been updated since this time in light of new evidence.
23. How do data on real-world experience compare with the trial data?	Real world data support the clinical trial data, demonstrating the utility of natalizumab when used for those with ongoing disease activity on first line treatment, not restricted to those with RES MS on first line treatment.
24. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.	There are substantial equalities issues supporting this MTA. As detailed above, we had been working with NHSE to extend the scope of use of natalizumab in those with highly active MS not meeting RES criteria for the purposes of pregnancy planning via a priority workstream within the PPP pathway. However, this MTA has paused this work.

Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	At present, there are a cohort of people with MS who are denied access to highly active therapy with proven safety data in pregnancy (those who have highly active MS whilst on antiCD20 therapy) – all other escalation options need to be stopped prior to conception, or are induction therapies mandating a full course with wash out, thus delaying pregnancy plans. For those who do not meet the criteria of RES MS and do not want exposure to immunosuppressive therapy during pregnancy (itself an immunosuppressed state), the options are either platform injectable therapy or no treatment. This is not the case for those who are not planning pregnancy, where a range of potentially teratogenic DMT are available, which would not be suitable to take during pregnancy planning. Widening access to natalizumab will have benefits related to improved MS care in and around pregnancy that will not be included in the QALY calculations. These issues specifically relate to the differential positioning of natalizumab as a second line/escalation therapy with use restricted only to those with RES MS compared to all other second line treatment options. There is no trial based rationale for this difference, and it is not supported by real world data. This reflects a specific equalities issue for this cohort of patients.
25. Would subcutaneous and intravenous formulations of natalizumab be used interchangeably? • If not, in whom would each formulation be used? • Would you expect different outcomes for different formulations?	We have no reason to expect that different formulations of natalizumab would be associated with different clinical outcomes. Once patients are established on a dose formulation of natalizumab they would not usually switch repeatedly, although may do so occasionally for reasons including patient preference,

26. What criteria would be used to define highly active relapsing remitting multiple sclerosis in clinical practice? • Is data from other forms of MS generalisable to the RRMS population? If not, why not?	Criteria used in other DMTs would be used to define highly active MS in this population. This would bring this TA into line with both the natalizumab clinical trials data and other TAs for MS treatments used in highly active disease. We would anticipate, for the purposes of this TA, for highly active MS on first line treatment to be defined as unchanged relapse rate or breakthrough disease despite a full course of DMT defined using standard clinical and MRI criteria.

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Natalizumab is a highly effective non-immunosuppressive treatment for MS.

Current commissioning arrangements mean that patients are forced to wait for a second, potentially disabling relapse prior to escalation to natalizumab from first line treatments, an approach not supported by trials or real-world data.

This restriction means that those with active disease controlled on non-pregnancy compatible treatments are being denied natalizumab, and potentially forced to de-escalate to less effective treatment than they are currently taking in order to access pregnancy-compatible treatments. This inequality must be addressed.

Risk management strategies are well established with natalizumab, both reducing risk and targeting intensive monitoring to where it is most needed.

This TA has the potential to improve quality of life, reduce the risk of disabling relapses, enable those with protected characteristics equitable access to highly effective therapies, and simplify DMT commissioning pathways, reducing strain on MDTs alongside clear patient benefit.

Thank you for your time.

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Natalizumab and Tyruko (natalizumab biosimilar) for treating highly active relapsing-remitting multiple sclerosis after at least one disease modifying therapy: a systematic review and economic model

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

Keywords

Multiple Sclerosis; Systematic Reviews; Network Meta-analysis; Economic model

Abstract

Background

Multiple sclerosis (MS) is an immune-mediated inflammatory disease, causing long-term disability in young adults. Most cases begin as relapsing-remitting MS (RRMS). Some people have a form of RRMS known as highly active RRMS (HARRMS), defined as MS with unchanged or increased disease activity despite prior treatment with at least one disease-modifying therapy (DMT).

Objectives

To appraise the clinical and cost effectiveness of natalizumab (Tysabri) and natalizumab biosimilar (Tyruko) for treating HARRMS compared to other DMT.

Design

Systematic review with network meta-analysis (NMA) and economic model.

Results

We included 42 studies (22, 409 participants): 40 in people with RRMS and two in HARRMS. Six studies also reported data separately for HARRMS. Only four studies evaluated natalizumab or natalizumab biosimilar; none provided data on those with HARRMS. Follow-up ranged from 4 to 36 (median 24) months.

Most interventions reduced relapses (39 studies, 17 interventions) and MRI lesions (19 studies, 11 interventions for Gd+ lesions and 17 studies, 12 interventions for T2 weighted lesions) compared to placebo. Alemtuzumab, ocrelizumab, natalizumab, fingolimod and peginterferon beta 1a reduced disease progression compared to placebo (15 studies, 12 interventions). There were no differences in any adverse events (AEs) (24 studies, 16 interventions), serious AEs (30 studies, 14 interventions) or treatment related AEs (8 studies, no NMA) for any intervention compared to placebo. Fingolimod, glatiramer acetate, interferon beta 1a, interferon beta 1b and peginterferon beta 1a were associated with an increased treatment discontinuation (29 studies, 13 interventions). There was little evidence for a difference in quality of life. There was no evidence of a difference between natalizumab and natalizumab biosimilar for relapse rates (RR 0.65 (95% credible interval (CrI) 0.33, 1.23), Gd+ lesions (HR 1.29 (0.69, 2.37), T2 weighted lesions (HR 1.07 (0.73, 1.57)), any AEs (HR 1.06 (0.77, 1.46) or treatment discontinuation (HR 0.48 (0.13, 1.76)).

Data in HARRMS were available for fingolimod, ocrelizumab, alemtuzumab, cladribine, beta-interferon, AHSCT, and placebo. We also included one study on natalizumab conducted in a population that was close to our definition of HARRMS. All interventions except interferon beta 1a were associated with reduced relapse risk compared to placebo (6 studies; 7 interventions).

Compared with natalizumab-IV, natalizumab biosimilar-IV and natalizumab-SC, all treatments had greater net benefit at £20-30,000/QALY, with the only exception being ocrelizumab which had lower net benefits. Costs were generally higher on natalizumab than other treatments, though there was no difference in QALYs with 95% CrI completely overlapping. The results and conclusions were unchanged under all sensitivities. Value of information analysis found that the greatest contributor to decision uncertainty was the effectiveness of treatments.

Conclusions

There is no direct evidence on the effectiveness of natalizumab or its biosimilar in patients with HARRMS. Limited data suggest similar effectiveness in patients with RRMS. The economic model found that natalizumab and natalizumab biosimilar were not cost-effective compared to any of the included comparators in HARRMS, with the only exception being ocrelizumab.

Future work

There is need for studies of natalizumab and natalizumab biosimilar in people with HARRMS.

Study registration

The review was registered at PROSPERO (CRD42024556838).

Funding

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List of Abbreviations

Term	Definition
AE	Adverse Event
AHSCT	Autologous Haematopoietic Stem Cell Treatment
AI	Artificial Intelligence
APDDS	Adapted Patient Determined Disease Steps
ARR	Annualised Relapse Rate
AV	Atrioventricular
BCEA	Bayesian Cost-Effectiveness Analysis
BGR	Brookes-Gelman-Rubin
BNF	British National Formulary
CBA	Cost-Benefit Analysis
CC	Complication and Comorbidity
CDP	Confirmed Disease Progression
CE	Cost-Effectiveness
CEA	Cost-Effectiveness Analysis
CEAC	Cost-Effectiveness Acceptability Curve
CEAF	Cost-Effectiveness Acceptability Frontier
CI	Confidence interval
CMA	Cost-Minimisation Analysis
CNS	Central Nervous System
CRD	Centre for Reviews and Dissemination
CrI	Credible Interval
CSF	Cerebrospinal Fluid
CUA	Cost-Utility Analysis
DCP	Disease Control Priorities
DES	Discrete Event Simulation
DESCEM	Discrete Event Simulation for Cost-Effectiveness Modeling
DIC	Deviance Information Criterion
DMD	Disease-Modifying Drug
DMT	Disease-Modifying Therapy
DP	Determiner Phrase
DSU	Decision Support Unit
EAG	External Assessment Group
EED	Economics Evaluations Database
EDSS	Expanded Disability Scale Status
EQ-5D	EuroQol 5 dimensions quality of life index
EBV	Epstein-Barr virus
EVPPI	Expected Value of Partial Perfect Information
FDA	Federal Drugs Agency
GP	Gaussian processes
GAM	Generalised Additive Models
GBP	Great Britain Pound
GBT	Generative Pre-Trained Transformer
HADS	Hospital Anxiety and Depression Scale

Term	Definition
HARRMS	Highly active relapsing remitting multiple sclerosis
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HLA	Human Leukocyte Antigen
HPV	Human Papillomavirus
HR	Hazard Ratio
HRG	Healthcare Resource Group
HRQoL	Health Related Quality of Life
HS	Health State
HTA	Health Technology Assessment
ICER	Incremental Cost-Effectiveness Ratio
ICTRP	International Clinical Trials Registry Platform
IFNB	Interferon beta
IQR	Interquartile range
ISPOR	International Society for Outcomes Research
ITT	Intention to treat
IM	Intramuscular injection
IV	Intravenous
JC	John Cunningham human polyomavirus
LCI	Lower Confidence Interval
MCMC	Markov Chain Monte Carlo
MD	Mean Difference
MLMC	Multilevel Monte Carlo
MPES	Multiparameter evidence synthesis
MRI	Magnetic Resonance Imaging
MS	Multiple Sclerosis
NA	Not Applicable
NCT	National Clinical Trial
NHS	National Health Service
NHS EED	NHS Economic Evaluations Database
NI	No information
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
NMA	Network Meta-Analysis
NR	Not Reported
PCR	Polymerase chain reaction
PICO	Patient, Population or Problem; Intervention; Comparison; Outcome (Cochrane)
PML	Progressive Multifocal Leucoencephalopathy
POCT	Point-Of-Care-Testing
PPMS	Primary Progressive Multiple Sclerosis
QALY	Quality Adjusted Life Year
QoL	Quality of Life
RCT	Randomized Controlled Trial
RES RRMS	Rapidly Evolving Severe Relapse Remitting Multiple Sclerosis

Term	Definition
RR	Rate Ratio
RRMS	Relapse Remitting Multiple Sclerosis
SAD	Sustained Accumulation of Disability
SC	Subcutaneous injection
SD	Standard deviation
SE	Standard error
SF-36	Self-Reported-36 quality of life index
SLR	Systematic Literature Review
SMDM	Society for Medical Decision Making
SOT RRMS	Sub-Optimally Treated Relapse Remitting Multiple Sclerosis
SPMS	Secondary Progressive Multiple Sclerosis
TA	Technology Appraisal
TAG	Technology Assessment Group
TIA	Transient Ischaemic Attack
TSD	Technical Support Document
UCI	Upper confidence interval
UK	United Kingdom
UME	Unrelated Mean Effects
UVB	Ultraviolet B light
VEP	Visually Evoked Potential
VOI	Value-Of-Information
WTP	Willingness-To-Pay
WHO	World Health Organisation

Plain English Summary

What is the problem?

Multiple sclerosis (MS) is a common lifelong condition affecting the brain and spine. It can cause symptoms like vision problems, trouble with balance, movement, thinking, and bladder or bowel control. MS often starts in early adulthood and usually worsens over time, though this varies.

The exact cause of MS is unclear, but factors like genetics, vitamin D levels, inflammation, smoking, and viral infections may increase the risk. Treatments can manage symptoms, slow disease progression, and improve quality of life.

Most people with MS have relapsing-remitting MS (RRMS), marked by relapses—periods when symptoms worsen or new ones appear, lasting weeks or months. Symptoms may improve after a relapse but often leave lasting effects. Some patients, known as having "highly active RRMS (HARRMS)", continue to have relapses despite treatment and may need different medications.

What did we do?

We wanted to know whether a drug called natalizumab (Tysabri) and similar drug known as natalizumab biosimilar (Tyruko) are effective and safe for patients with HARRMS, when compared with other drugs already in use for these patients. We also wanted to know whether using these drugs is a good use of NHS money. We looked at existing research and developed cost models to answer these questions.

What did we find?

No studies were found that specifically evaluated Tysabri or Tyruko in people with HARRMS. However, four studies in people with RRMS showed these drugs seemed equally effective for this group. Evidence from other treatments suggests that drugs effective in general RRMS also work well in HARRMS, so it's reasonable to expect that Tysabri and Tyruko might have similar results for these patients. However, evidence from our cost model suggested that these drugs do not represent good value for money compared to other treatments for MS.

Word count: 271

Scientific Summary

Background

Multiple sclerosis (MS) is a chronic autoimmune condition that affects the central nervous system, usually starting in early adulthood and often causing long-term disability in young adults. Symptoms can vary but commonly include fatigue, muscle weakness, vision problems, and cognitive issues. In the UK, around 130 in every 100,000 people are affected. Most cases (85–90%) begin as relapsing-remitting MS (RRMS), with periods of relapses and remissions, which can later progress to secondary progressive MS (SPMS). A smaller group have primary progressive MS (PPMS) from the start. RRMS can be further categorised based on disease activity. Highly active RRMS (HARRMS), the focus of this appraisal, is broadly defined as MS with unchanged or increased disease activity—clinically or radiologically—despite prior treatment with at least one disease-modifying therapy (DMT). Management typically includes multidisciplinary care and DMTs to reduce relapses and slow progression.

Objectives

The overall aim was to appraise the clinical and cost effectiveness of natalizumab (Tysabri) and natalizumab biosimilar (Tyruko) within their marketing authorisations for treating HARRMS after at least one disease modifying therapy.

Methods

Clinical effectiveness review

We conducted a systematic literature review (SLR) with network meta-analysis (NMA). As we did not expect to find many RCTs in people with HARRMS, we broadened inclusion to people with RRMS. We included RCTs that compared one of the interventions (natalizumab or natalizumab biosimilar) or comparators of interest (glatiramer acetate, interferon beta-1a, interferon beta-1b, peginterferon beta-1a, alemtuzumab, cladribine tablets, fingolimod, ocrelizumab, ofatumumab, ponesimod, and AHSCT) to each other or to placebo.

We searched MEDLINE, EMBASE and trial registries from inception to April 2024. We screened existing relevant technology appraisals, SLRs and submissions from manufacturers of natalizumab and natalizumab biosimilar.

Title and abstract screening and assessment of full text papers were conducted by two reviewers independently. Data extraction and risk of bias assessment were performed by one reviewer and checked by a second. Risk of bias was assessed with the RoB 2 tool at the outcome level. We extracted and synthesized data on the following outcomes:

- Annualised relapse rate (ARR)
- Disability progression confirmed at 3 and 6 months (CDP3 and CDP6)
- MRI measurements (proportion of participants with gadolinium enhancing (Gd+) or new or enlarging T2 lesions)
- Adverse effects (AEs) of treatment (any AEs, treatment related AEs, serious AEs, AEs leading to treatment discontinuation)
- Health-related quality of life assessed using the EQ-5D or SF-36 scales

For each outcome, we provided a narrative summary of study details, risk of bias, and results. Bayesian random and fixed effects NMA was performed to compare the efficacy and safety of treatment options using the available trial information. Most treatments were not compared in head-to-head RCTs, and NMA allowed for the use of indirect information to make that comparison. We selected the model (random vs fixed effects) that provided the best fit to the data. We presented results as comparisons of each intervention in the network with placebo, mean ranking of each intervention, probability that each intervention would rank first or in specific positions, and a pairwise comparison of each intervention included in the network. Bayesian 95% credible intervals (CrI) were used to represent uncertainty. We used the R package 'multinma' for all analyses.

Cost-effectiveness

We undertook an independent economic assessment using a Discrete Event Simulation (DES) individual patient model. Previous NICE Technology Assessments (TAs) have been criticised as they did not capture treatment sequencing and that they were unable to accurately reflect the course of the condition. Our DES aimed to overcome these limitations by using by modelling of treatment sequences

To design the model, we reviewed models used in previous NICE TAs. These used very similar Markov multistate models based on EDSS severity with transition rates informed by the British Columbia Multiple Sclerosis registry and London Ontario MS databases and treatment effects by individual trials and NMA. Our DES modelled EDSS as an individual attribute, aligning with the structure of the prior models. We also included attributes for age, sex, SPMS status and current treatment. Simulated events were EDSS increase, EDSS decrease, SPMS progression, relapse, SAEs, treatment discontinuation, and death. Patients could switch treatment twice, meaning that up to 4th line therapy was modelled. Patients who progressed SPMS could experience the events EDSS increase, relapse, SAEs, and death.

Event rates were informed by a combination of new analyses conducted by the UK MS Registry and treatment effects of ARR and CDP6 estimated by the NMA. Baseline SAEs and discontinuation came from AFFIRM and ANTELOPE with treatment effects from the NMA. Rates in the SPMS population were informed by the MS Registry analyses as no treatment effects were assumed. Our approach to costs and utilities were aligned with previous TAs. The cost of John Cunningham human polyomavirus (JCV) testing was included for both natalizumab and natalizumab biosimilar as clinical advice was that the manufacturer scheme of paying for JCV testing is not widely available. The economic model was implemented in the R programming language using the DESCEM package and the code was validated by an independent analyst at the consultancy Evidera. The model precited EDSS severity over time was validated by comparison to a Markov model prediction.

The selected base case analysis used the HARRMS population from the MS Registry for baseline rates and the base case selection from the NMA results. Sensitivity analyses were conducted using the All RRMS estimates from the MS Registry, switching to alternative NMA sensitivities, excluding the price of JCV testing for natalizumab-IV and natalizumab-SC (not

the biosimilar), reducing the natalizumab-SC treatment administration costs, and using mortality rates that vary with EDSS. Value of information analysis was used to assess the impact on parameter uncertainty and identify the most influential parameters. The Expected Value of Partial Perfect Information (EVPPI) was estimated for each of the NMA treatment effects, all costs, all utilities, the MS registry baseline rates, the baseline discontinuation rate, and the baseline SAE rate.

Results

We included 42 studies (22, 409 participants): 40 reported data for a general RRMS population and two were conducted in HARRMS. Six studies reported data separately for those with HARRMS. Only four studies evaluated Natalizumab or Natalizumab biosimilar, the technologies of interest for this appraisal; none provided data on those with HARRMS. AHSCT was only evaluated in people with HARRMS.

General RRMS population

All studies were considered to be sufficiently similar for inclusion in the NMAs. The fixed effect model gave the best fit to the data with little evidence of heterogeneity for all outcomes.

ARR (39 studies, 20, 810 participants; 17 interventions)

Follow-up ranged from 4 to 36 (median 24) months. Most interventions were associated with a greater reduction in the risk of relapses compared to placebo (i.e., RR<1 AND 95% CrI excluding 1.00). There was no evidence of a difference between natalizumab and natalizumab biosimilar (RR 0.65 (95% CrI 0.33, 1.23). Seventeen (44%) studies were at low risk of bias, 15 (38%) had some concerns regarding risk of bias, and 7 (18%) were at high risk of bias. Sensitivity analysis restricted to studies at low risk of bias showed similar results.

Disease Progression (23 studies; 12 interventions)

Studies on teriflunomide, ponesimod and ofatumumab did not connect to the network and studies of natalizumab biosimilar and glatiramer acetate SC40 did not report on disease progression, and those on interferon beta 1a SC22 only reported data on CDP3. Fifteen studies (10, 635 participants; 11 interventions) reported CDP3 and fourteen studies (9,306 participants; 10 interventions) reported CDP6. Alemtuzumab, ocrelizumab, natalizumab, fingolimod and peginterferon beta 1a were associated with a lower risk of both CDP3 and CDP6. Six studies were judged at low risk of bias, nine at some concerns and five at high risk of bias.

MRI Outcomes (20 studies; 12 interventions)

Follow-up ranged from 4 to 24 (median 24) months. There were no data on MRI outcomes for studies of ofatumumab, glatiramer acetate (SC40), ponesimod, teriflunomide, and peginterferon beta 1a. Data were only available for T2 lesions for interferon beta 1a (SC22).

Nineteen studies (9, 471 participants; 11 interventions) reported data on Gd+ lesions and seventeen studies (8,883 participants; 12 interventions) on T2 weighted lesions. All interventions were associated with a greater reduction in the risk of developing MRI lesions compared to placebo, with the exception of interferon beta 1a SC44 for T2 weighted lesions. There was no evidence of a difference between natalizumab and natalizumab biosimilar (HR 1.29 (0.69, 2.37) for Gd+ lesions or for T2 weighted lesions (HR 1.07 (0.73, 1.57)).

Adverse events (36 studies)

Follow-up ranged from 6 to 24 months (median 18 months) follow-up. Twenty four studies (9, 471 participants; 16 interventions) reported data on **any adverse events** – data were not available for interferon beta 1a (SC22). Thirty studies (18, 748 participants; 14 interventions) reported data on **SAEs** – data were not available for interferon beta 1a (SC22), cladribine or natalizumab biosimilar. There was no evidence of a difference in the risk of developing any AEs or serious AEs between any of the interventions and placebo. There was no evidence of a difference between natalizumab and natalizumab biosimilar 1.06 (0.77, 1.46) in the risk of any AEs; data were not available for serious AEs. Only eight studies (n=3,361) reported data on **treatment related adverse events**. These did not create a connected network and so an NMA was not possible. There was no evidence of a difference in AEs within any of the studies.

Twenty nine studies (17,892 participants) reported data on **AEs leading to treatment discontinuation**. These did not create a completely connected network – teriflunomide, ponesimod and ofatumumab did not connect to the network and data were not available for interferon beta 1a (SC22). Fingolimod, glatiramer acetate, interferon beta 1a, interferon beta 1b and peginterferon beta 1a were associated with an increased risk of treatment discontinuation compared with placebo. There was no evidence of a difference between natalizumab and natalizumab biosimilar (HR 0.48 (0.13, 1.76)).

Twenty studies were judged at low risk of bias for adverse events, eleven at some concerns and five at high risk of bias.

Quality of life

Only eight studies reported quality of life assessed using the EQ-5D or SF-36 tools. Interventions evaluated were cladribine, fingolimod, peginterferon beta and glatiramer acetate vs placebo and alemtuzumab vs interferon beta 1a. There was little evidence for a difference in quality of life in any of these studies.

HARRMS population

We had data for 6 studies that evaluated fingolimod, ocrelizumab, alemtuzumab, cladribine, beta-interferon, AHSCT, and placebo in people with HARRMS. Three studies were at high risk of bias, one had some concerns, and two were low-risk.

Five studies reported data on ARR. As there were no studies on natalizumab in people with HARRMS, we included one study that compared natalizumab with placebo in a population where participants were required to have had at least one relapse in the previous year and a very high proportion of participants (88%) had previously been treated with a DMT. A connected network for ARR was formed by combining two interferon beta 1a comparators. The network included six studies (2,162 participants) of seven interventions. All interventions except interferon beta 1a, were associated with a reduced ARR compared to placebo, with natalizumab and ocrelizumab ranking highest.

As we only had data on a limited number of interventions in HARRMS, to allow direct comparisons between RRMS and highly active populations, we conducted a sensitivity analysis in RRMS where we restricted the network to the eight interventions in the network for ARR in the highly active population. Results were very similar, although 95% CrI were wider in the highly active population. CDP data were limited and disconnected, but all evaluated interventions reduced progression risk. MRI, QoL and adverse events outcomes were only evaluated in one or two studies and so there was insufficient information on these outcomes to draw conclusions.

Cost-effectiveness

The clinical review found no evidence on autologous haematopoietic stem cell transplantation so this was not included in the economic model. The NMA estimates in all RRMS were used for treatment effects on CDP6, ARR, SAEs, and discontinuation due to AEs, as only limited data were found for HARRMS.

Base case results used 1000 patients and 1000 samples while sensitivities used 100 patients and 100 samples; the lower number were found sufficient for stable results by convergence checks. Validation of EDSS severity over time found less severe trend that was explained by the comparator model mixing RRMS and SPMS patients and not using the latest DMT sequences.

Compared with natalizumab-IV, natalizumab biosimilar-IV and natalizumab-SC, all treatments had greater net benefit at £20-30,000/QALY, with the only exception being ocrelizumab. The natalizumabs had close to 0% chance of having highest net benefit at £20-30,000/QALY. Costs were generally higher on natalizumab than other treatments, though there was no difference in QALYs with 95% CrI overlapping. Natalizumab-IV has lower mean net benefit at £20-30,000/QALY than natalizumab biosimilar-IV, although the 95% CrI overlap. Natalizumab-SC has very similar mean net benefit to Natalizumab-IV. The 95% CrI for costs and QALYs on natalizumab biosimilar-IV also overlapped with those for natalizumab-IV suggesting no difference. Natalizumab-SC has very similar costs and QALYs to natalizumab-IV, again with no evidence of a difference.

Conclusions were unchanged under all sensitivities. EVPPI estimates indicated the parameters with greatest impact were the NMA treatment effects on ARR, CDP6, SAEs, and

discontinuation. However, costs, utilities, and MS registry rates, also had substantial impact on the results indicating high parameter uncertainty.

Conclusions

There is no direct evidence on the effectiveness of natalizumab or its biosimilar in patients with highly active disease. Limited data indicate that both treatments show similar effectiveness in patients with RRMS. Comparisons of DMT effectiveness in people with highly active disease and general RRMS suggest that DMTs are at least as effective in the highly active population, although this is based on sparse data. Assuming natalizumab and its biosimilar follow this trend, they may also be effective in this group. However, trials specifically targeting this population are needed to confirm these assumptions.

The economic model used evidence on treatment effects in the general RRMS population and baseline rates in highly active RRMS. Natalizumab-IV, natalizumab biosimilar-IV and natalizumab-SC were not cost-effective compared to any of the included comparators in highly active RRMS, with the only exception being ocrelizumab. The greatest decision uncertainty was found in the treatment effects, again supporting the need for trials targeting this population.

Study registration

The review was registered at PROSPERO (CRD42024556838).

Funding

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Word count: 2400 words

1 Background

Sections of this Chapter have been reproduced from the study's Protocol document, available at the NICE website.[1]

1.1 Multiple sclerosis

Multiple sclerosis (MS) is a chronic, inflammatory, neurological immune mediated inflammatory disease that affects the central nervous system (CNS), which includes the brain and spinal cord.[2] MS usually presents in early adult life and is the most common cause of non-traumatic disabling disease in young adults.[2-4] In MS, the immune system mistakenly attacks the protective covering of nerve fibres called myelin, causing inflammation and damage. This disrupts the normal flow of electrical impulses along the nerves. Inflammation can also lead directly to damage to axons, leading to their degeneration or loss. Axonal loss contributes significantly to the neurological symptoms and disability observed in people with MS.

The symptoms of MS vary widely and can include bladder and bowel dysfunction, cognitive changes, gait disturbance, fatigue, muscle weakness, numbness or tingling, difficulty with coordination and balance, and problems with vision.[2, 3]. It is not clear what causes MS, but a number of theories have been proposed. These include the “outside in” and “inside out” pathways. With the “outside in” model it is hypothesised that an unknown factor triggers the autoimmune response peripherally (outside the Central Nervous System (CNS)), instigating the immune system to begin to invade the CNS, starting the process of demyelination characteristic of MS. The “inside out” model suggest that primary damage of the myelin as the cause of MS, leading to an autoimmune attack which results in further inflammatory demyelination.[5] A number of factors have been associated with the risk of developing MS, these include genetic abnormalities, environmental factors such as vitamin D or ultraviolet B light (UVB) exposure, obesity, smoking and viral infection.[5, 6] More recently a compelling link has been established between Epstein-Barr virus (EBV) and MS – being negative for EBV protects against MS, whereas a history of exposure doubles the risk of developing MS.[6, 7] A number of genes have been found to be associated with MS. The main genetic risk is with the Human Leukocyte Antigen (HLA) HLA-DRB1*15, although genome wide association studies have identified over 200 independent genome-wide significant associations outside the major histocompatibility complex (MHC) and 32 within the MHC region and over 550 candidate risk genes.[8]

MS has a significant impact on individuals' quality of life and imposes a substantial burden on healthcare systems and society as a whole.[3] A recent cross-sectional study of almost 17,000 participants with MS from across 16 countries found that work capacity declined from 82% to 8%, and that quality of life declined from normal population values to less than zero, indicating that the negative aspects of an individual’s life outweigh the positive impacts, as disability became more severe with advancing disease.[3] MS may reduce life expectancy with a recent study estimating life expectancy to be 75.9 years in an MS population compared to 83.4 years in a population matched on sex, age, and region.[9] While

there is currently no cure for MS, treatments are available to help manage symptoms, slow disease progression, and improve quality of life for individuals with MS.

1.2 Epidemiology of MS

MS is estimated to have a global prevalence of over 2.8 million cases (35.6 per 100 000 population), although this may be an underestimate due to the lack of data from large populations including China and India.[10] Incidence and prevalence is increasing in both developed and developing countries.[10]

Estimates of incidence vary across studies, with higher prevalence rates observed in regions further from the equator, particularly in Europe, North America, and parts of Australasia.[4, 6] A 2020 multi-national study reported a pooled incidence rate across 75 studies that provided data as 2.1 per 100 000 persons/year.[10] The prevalence of MS tends to increase with distance from the equator, although there are exceptions to this pattern.[6] The reasons for this geographic variation are not fully understood but may involve a combination of genetic, environmental, and lifestyle factors. Distance from the equator is also associated with UVB exposure which stimulates vitamin D production – low levels of vitamin D have been associated with MS.[6] Migration studies have shown that migrants from low risk countries (e.g. the West Indies) to Europe remain at low risk of developing MS, however children born to migrants in Europe are at high risk.[6] This suggests that environment over-rules genetics, suggesting that prevention should focus on environmental risk factors.

In the United Kingdom (UK), MS is a relatively common neurological condition, with an estimated prevalence of around 130 cases per 100,000 population, with an estimated 7,000 new cases each year.[11] The prevalence of MS in the UK is among the highest in Europe. MS affects people of all ages, but it is most commonly diagnosed in young adults, typically between the ages of 20 and 40. Women are about two to three times more likely to develop MS than men, although in the early 1900s the sex ratio was almost equal.[6] A reason for this change may be the changing prevalence of smoking in women over time – before the first world war very few women smoked. The incidence and prevalence of MS in the UK have been increasing over time, although this trend may be partially attributed to improvements in diagnostic methods and increased awareness of the condition.

1.3 Clinical pathway

1.3.1 Clinical presentation

MS is usually first suspected when a patient presents with what is known as a “clinically isolated syndrome” (CIS), this occurs as result of lesions in the brain or spinal cord and presentation will depend on the location of the lesion. The most frequent presentations include unilateral optic neuritis, brainstem syndromes (e.g. intranuclear ophthalmoplegia, vertigo, hearing loss, facial sensory disturbance) and focal sensory disturbance (e.g. limb paresthesias) although many other presentations exist.[6, 12]

1.3.2 Diagnosis of multiple sclerosis

The diagnosis of multiple sclerosis (MS) is primarily a clinical diagnosis, supported by investigations including imaging and cerebrospinal fluid (CSF) analysis. The key features required for a diagnosis of MS are dissemination in time and space – this involves looking for evidence of disease activity affecting different parts of the CNS across different points in time. Differential diagnosis of MS can be challenging, particularly in the early stages, as many other disorders have similar clinical presentations and paraclinical findings to MS.[13] The 2022 NICE guidelines on the diagnosis and management of MS recommend that people suspected of having MS should be referred for diagnosis by a consultant neurologist or specialist under their supervision.[14]

Diagnostic criteria have evolved over time from the first criteria proposed by Jean-Martin Charcot as early as 1868[15] to the most recently published 2017 McDonald criteria.[16] The McDonald criteria were first developed by an international committee of neurologists and published in 2001.[17] These were updated in 2005, 2010 and most recently in 2017[16] – these are the current criteria recommended for diagnosis of MS by NICE. A 2024 update was announced at the recent ECTRIMS 2024 conference,[18] but these have not yet been published. These are expected to allow for an earlier diagnosis than previous versions of the criteria. Table 1 provides an overview of the 2017 McDonald criteria for diagnosing MS. These follow the principle of aiming to detect evidence of dissemination in time and space.

Table 1 2017 Revised McDonald criteria for diagnosing MS[16]

Number of attacks at clinical presentation	Number of lesions with objective clinical evidence	Additional data needed for diagnosis of MS
≥2	≥2	None
≥2	1 + clear cut historical evidence of a previous attacking involving a lesion in a distinct anatomical location	None
≥2	1	Dissemination in space demonstrated by additional clinical attack implicating a different CNS site *OR* by MRI
1	≥2	Dissemination in time demonstrated by an additional clinical attack *OR* by MRI *OR* demonstration of CSF-specific oligoclonal bands
1	1	Dissemination in space demonstrated by an additional clinical attack implicating a different CNS site OR by MRI AND Dissemination in time demonstrated by an additional clinical attack OR by MRI OR demonstration of CSF-specific oligoclonal bands

Magnetic resonance imaging (MRI) can be used to detect changes in white matter lesions in the brain. It is not sufficiently accurate to be used alone for the diagnosis of MS, but can be helpful in addition to clinical features.[19] CSF analysis involves detection of oligoclonal bands as a surrogate marker of dissemination in space.[20] The presence of oligoclonal bands (bands of immunoglobulin) provides evidence of local immunoglobulin synthesis which occurs most commonly in MS, but can also be found in other conditions and so the finding is not specific for the diagnosis of MS.[21] Findings of elevated CSF protein or significant pleocytosis or the presence of neutrophils is not typical of MS and so suggests an alternative diagnosis. The McDonald 2017 criteria allow for a greater role of MRI and CSF than previous versions, allowing for an earlier diagnosis of MS. This is particularly important as new, earlier aggressive treatments become available for MS; it is important to identify patients with MS so that they can receive treatment as soon as possible, but it is equally important that people are not wrongly diagnosed with MS and given inappropriate treatment with these aggressive treatments.[22] Visually evoked potentials (VEP) have previously been suggested as useful for the diagnosis of MS. These are electrical signals recorded from the brain's occipital lobe in response to visual stimuli, used to assess the integrity of visual pathways, with an abnormal VEP suggesting a second lesion if the clinical presentation did not include the visual pathway. However, these are not included in the current diagnostic criteria due to insufficient evidence.[23]

1.3.3 Measurement of progression

Disease activity and progression are measured using MRI activity, incidence of relapses and short-term (3-6 month) progression in disability.[12] MRI measures of disease activity include the development of new T2 lesions, enlarging T2 lesions, and gadolinium-enhancing lesions. T2 lesions are areas of abnormal signal intensity seen on T2-weighted MRI scans, commonly indicating water content or inflammation in tissues. In MS, T2 lesions often represent areas of demyelination or damage in the brain and spinal cord, providing insights into disease activity and progression. Gadolinium-enhancing lesions are areas of the brain that show increased uptake of gadolinium-based contrast dye during MRI scans, indicating active inflammation. These lesions are used to identify active disease processes, distinguish new lesions from older ones, and to monitor treatment response. Disability is measured using the Expanded Disability Status Scale (EDSS) – this quantifies the accumulation of permanent disability. Scores range from 0 (no disability) to 10 (death) and are measured in incremental units of 0.5 (from EDSS 1). Scores are based on measures of impairment across the eight functional symptoms:[24]

1. Pyramidal Functions: weakness or difficulty in moving limbs
2. Cerebellar Functions: ataxia, loss of coordination, or tremor
3. Brain Stem Functions: problems with speech, swallowing, and nystagmus involuntary eye movement)
4. Sensory Functions: numbness or loss of sensations
5. Bowel and Bladder Functions
6. Visual (or Optic) functions
7. Cerebral (or Mental) Functions

8. Other Functions (neurologic findings)

To provide an accurate and reliable evaluation of confirmed disability progression (CDP), two consecutive examinations should be carried out by the same physician at least 6 months apart. Although EDSS is commonly used it does not capture some important aspects of the impact of MS, particularly on quality of life. It is also prone to bias as it is a subjective measure and so open to investigator bias and is also heavily influenced by mobility.

1.3.4 Classification of MS

MS presents on a continuum from relapsing to progressive disease, with distinctions currently made between different types of disease. Some see this as an artificial distinction as they force cases into distinct boxes, which does not reflect the continuum of illness.[6] Most cases of MS (85-90%) are characterised by relapses followed by periods of remission – known as "relapsing remitting MS" (RRMS). A relapse generally develops over a period of hours to days, then reaches a plateau lasting several weeks, followed by a period of gradual recovery. The nature of the relapse is dependent on the region of the CNS affected by the acute demyelinating lesion, and also by the extent of the inflammation.[4] Although initial relapses can lead to complete recovery, there is often some damage left behind by the relapse, with overall disability increasing slightly after each relapse.[25] As neuronal damage increases, recovery from disability becomes incomplete leading to further disability.[6] RRMS is further subcategorised depending on disease activity and response to treatment. There is a lack of consensus regarding the definitions for the varying subtypes of disease, with different appraisals and studies using slightly different definitions. Table 2 provides an overview of the different subclassification of RRMS, with suggested definitions for each. The population of interest for this appraisal is "highly active disease" (highlighted blue in the table). We provide a very broad definition for this population to encompass most of the variety of different definitions used in existing appraisals and studies.

Table 2 Overview of subclassifications of RRMS[26]

Classification	Definition
Active disease	≥Two clinically significant relapses within the last 2 years. (Any motor relapse, any brainstem relapse, a sensory if it leads to functional impairment, a relapse leading to sphincter dysfunction, optic neuritis, intrusive pain lasting more than 48 hours)
Highly active disease	No consensus definition; previous appraisals for NICE have used different definitions. We will use the following broad definition for this appraisal to encompass the variety of different definitions used in existing trials: *Unchanged or increased clinical or radiological evidence of disease activity despite treatment with at least one Disease Modifying Therapy (DMT)*
Rapidly evolving severe (RES) disease	≥Two disabling relapses in 1 year and MRI changes (one or more gadolinium-enhancing lesions or a significant increase in T2 lesion load compared with a previous MRI). A disabling relapse is defined as any relapse which fulfils one or more of the following criteria: • Affects the patient's social life or occupation, or is otherwise considered disabling by the patient

Classification	Definition
	• Affects the patient's activities of daily living as assessed by an appropriate method • Affects motor or sensory function sufficiently to impair the capacity or reserve to care for themselves or others • Needs treatment/hospital admission.[26]

After 10-15 years RRMS typically develops into "secondary progressive MS" (SPMS), characterised by a gradual progression from discrete relapses to disease that progresses slowly.[23] A smaller proportion have a progressive onset from the start, known as "primary progressive MS" (PPMS). The proportion of patients with PPMS has decreased over time, but this may be an artificial change, caused by patients being more commonly labelled as having RRMS so that they are eligible for some of the newer treatments,[6] or be a result of better ascertainment of relapses leading to more people being identified as having RRMS. PPMS is more common in those presenting in later life (over age 60 years).[4]

1.3.5 Management of MS

Management of MS typically involves a multidisciplinary approach, including medical treatment to manage symptoms and modify disease progression, rehabilitation therapies, and support services to address the physical, cognitive, and emotional challenges associated with the condition. The pathway may vary depending on the subtype of MS, disease severity, individual patient factors, and treatment goals. The MS treatment pathway is dynamic and individualized, requiring ongoing collaboration between patients, healthcare providers, and interdisciplinary teams to optimize outcomes and quality of life for individuals living with MS. NICE guidelines recommend that people with MS should have a comprehensive review of all aspects of their care at least once a year.[12, 14]

Symptomatic management focuses on alleviating symptoms associated with MS, such as fatigue, mobility problems, spasticity, oscillopsia, emotional lability, pain, cognitive and memory problems, ataxia, tremor and dystonia. Symptomatic treatments may include medications, physical therapy, occupational therapy, speech therapy, cognitive rehabilitation, assistive devices, and lifestyle modifications.[14] Acutely, relapses are often treated with corticosteroids and, sometimes, plasma exchange.[27]

Disease-modifying therapies (DMTs) are the cornerstone of treatment for relapsing forms of MS. DMTs aim to reduce the frequency and severity of relapses, delay disability progression, and decrease the number of lesions observed on MRI scans.[12] They work by modifying the course of MS by supressing or modulating immune function. Various DMTs are available, including injectable medications, oral agents, and infusion therapies, each with different mechanisms of action and side effect profiles. Interferon beta-1b was the first DMT to be approved by the Federal Drugs Agency (FDA) in 1993. This was followed by interferon beta-1b and glatiramer acetate. These drugs were generally well tolerated and have a modest impact on the frequency of relapses.[28] Prior to this a variety of immunosuppressive agents

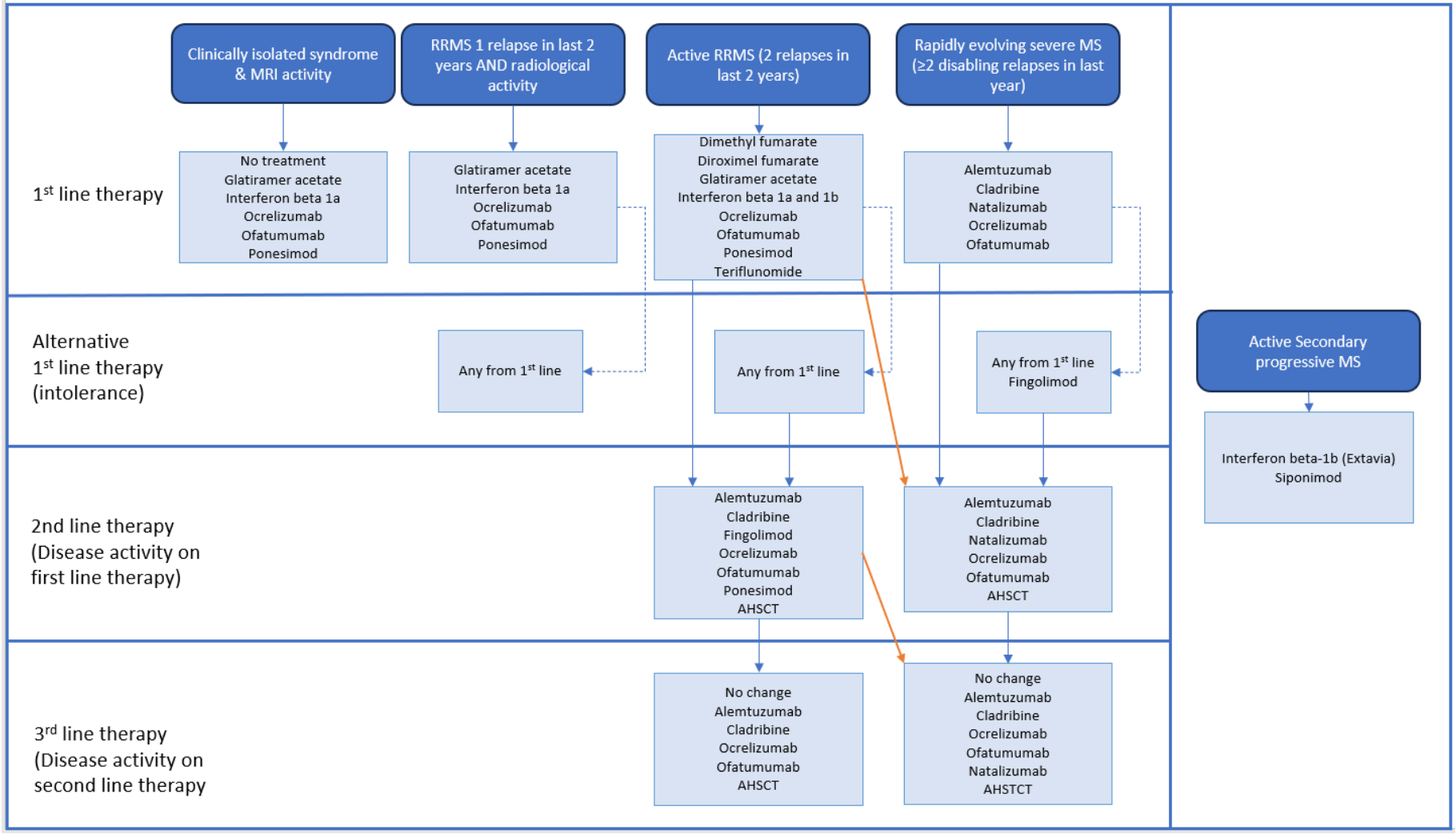
were used to treat MS including azathioprine, methotrexate, mycophenolate mofetil, intravenous immunoglobulin, and corticosteroids.[28]

More recently many MS specific DMTs have become available.[28] Table 3 provides an overview of the DMTs that have been appraised by NICE. It also highlights which DMTs are included in the scope for this appraisal – interventions and comparators are shown in cells shaded blue in the table, interventions are also highlighted in bold. NHS England have developed a treatment algorithm for DMTs within the NHS. Different treatment options are recommended based on initial presentation.[29] The recommendations for RRMS are summarized in Figure 1. An additional treatment option is *autologous haematopoietic stem cell transplantation*. This involves collecting a patient's healthy stem cells from the blood or bone marrow before treatment, storing this and then giving it back to the patient after treatment. A growing body of evidence suggests that this can induce prolonged remission in patients with RRMS.[28]

Patients who progress to SPMS are managed with Interferon beta-1b (Extavia) or Siponimod if they meet the following starting criteria:

- Patient is able to walk 10 m or more (EDSS less than 7.0)
- >18 years-old
- No contraindications
- Patient has been informed of and agreed to stopping criteria
- For Siponimod, there is also a requirement of active disease (relapses or imagine features of inflammatory activity).[30]

Figure 1 NHS England treatment algorithm for MS DMTs



Orange arrows show treatment pathways for patients with active RRMS who develop RES

AHSCT: autologous haematopoietic stem cell treatment.

Table 3 Overview of DMTs for adults with MS together with details of marketing authorisation and NICE recommendations

Pale blue highlighting shows interventions and comparators included within the scope of this appraisal

Drug name	Mechanism of Action	Administration route and frequency	Marketing authorisation	Related NICE TA	NICE recommendation
Recommended for RRMS					
Glatiramer Acetate	Not fully known	SC injection, once daily or 3 times weekly	Relapsing forms of multiple sclerosis.	TA527[31]	Recommended for treating RRMS
Interferon beta-1a	Not fully known	IM injection, once Weekly or SC injection, 3 times weekly	Relapsing multiple sclerosis. In clinical trials, this was characterised by two or more acute exacerbations (relapses) in the previous three years without evidence of continuous progression between relapses.	TA527[31]	Recommended for treating RRMS
Peginterferon beta-1a	Not fully known	SC injection, every 2 weeks	Relapsing remitting multiple sclerosis.	TA624[32]	Recommended for treating RRMS
Interferon beta-1b (Extavia)	Not fully known	SC injection, every other day	Relapsing remitting multiple sclerosis and two or more relapses within the last two years.	TA527[31]	Recommended for treating RRMS if person has had 2 or more relapses with past 2 years. *Currently not available in the UK*
Recommended for RRMS in specific situations or specific subtypes					
Ocrelizumab	Anti-CD20 mAb	IV infusion, every 6 months	Adult patients with relapsing forms of multiple sclerosis (RMS) with active disease defined by clinical or imaging features.	TA533[33]	Recommended for active RRMS only if alemtuzumab is contraindicated or otherwise unsuitable
Natalizumab (Tysabri)	α4β1 integrin inhibitor	IV infusion, every 4 weeks can also be given subcutaneously	Highly active RRMS: • Rapidly evolving severe RRMS defined by 2 or more disabling relapses in one year, and with 1	TA127[34]	Recommended for rapidly evolving severe RRMS

Drug name	Mechanism of Action	Administration route and frequency	Marketing authorisation	Related NICE TA	NICE recommendation
			or more Gadolinium enhancing lesions on brain Magnetic Resonance Imaging (MRI) or a significant increase in T2 lesion load as compared to a previous recent MRI. OR • Highly active disease despite a full and adequate course of treatment with at least one DMT		
Natalizumab biosimilar (Tyruko)	α4β1 integrin inhibitor	IV infusion, every 4 weeks	Highly active RRMS: • Rapidly evolving severe RRMS defined by 2 or more disabling relapses in one year, and with 1 or more Gadolinium enhancing lesions on brain Magnetic Resonance Imaging (MRI) or a significant increase in T2 lesion load as compared to a previous recent MRI. OR • Highly active disease despite a full and adequate course of treatment with at least one DMT	NA	Recommended as per Natalizumab (Tysabri) under NICE's biosimilar policy
Diroximel fumarate (Almirall)	Nuclear factor (erythroid derived 2)–like 2 pathway inhibitor	Oral, twice daily	Adult patients with relapsing–remitting multiple sclerosis.	TA794[35] TA320[36]	Recommended for active RRMS only if they do *not* have highly active or rapidly evolving severe relapsing–remitting multiple sclerosis
Dimethyl fumarate	Promotes anti-inflammatory activity and can	Oral, twice daily	Indicated for the treatment of adult patients with relapsing remitting multiple sclerosis	TA320[36]	Recommended for active RRMS, only if:

Drug name	Mechanism of Action	Administration route and frequency	Marketing authorisation	Related NICE TA	NICE recommendation
	inhibit expression of pro-inflammatory cytokines and adhesion molecules				they do not have highly active or rapidly evolving severe relapsing-remitting multiple sclerosis, and the manufacturer provides dimethyl fumarate with the discount agreed in the patient access scheme.
Teriflunomide	Inhibits the enzyme dihydroorotate dehydrogenase (DHODH)	Oral, 14 mg once daily	Approved for the treatment of RRMS in adults and children aged 10 years and older.	NICE TA303[37]	Recommended for active RRMS only if they do not have highly active or rapidly evolving severe RRMS and the manufacturer provides teriflunomide with the discount agreed in the patient access scheme.
Cladribine	Not fully known	Oral, 4-5 days over 2-week treatment courses	Adult patients with highly active relapsing multiple sclerosis (MS) as defined by clinical or imaging features	NICE TA616[38]	Recommended for highly active MS only if the person has rapidly evolving severe RRMS or disease that has responded inadequately to treatment with DMT
Recommended for previously treated RRMS					
Alemtuzumab	Anti-CD52 mAb	IV infusion, once daily	Adult patients with relapsing remitting multiple sclerosis (RRMS) with active disease defined by clinical or imaging features.	TA312[39]	Recommended for highly active RRMS despite a full and adequate course of treatment with at least 1 disease-modifying therapy OR rapidly evolving severe RRMS

Drug name	Mechanism of Action	Administration route and frequency	Marketing authorisation	Related NICE TA	NICE recommendation
Fingolimod	Sphingosine-1-phosphate inhibitor	Oral, once daily	Indicated as single disease modifying therapy in highly active relapsing remitting multiple sclerosis for the following adult patient groups: • Patients with highly active disease despite a full and adequate course of treatment with at least one disease modifying therapy or • Patients with rapidly evolving severe relapsing remitting multiple sclerosis defined by 2 or more disabling relapses in one year, and with 1 or more Gadolinium enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to a previous recent MRI	TA254[40]	Recommended for highly active RRMS if they have an unchanged or increased relapse rate or ongoing severe relapses compared with the previous year despite treatment with beta interferon
Ofatumumab	Anti-CD20 mAb	SC injection, every 4 weeks	Adult patients with relapsing forms of multiple sclerosis (RMS) with active disease defined by clinical or imaging features.	TA699[41]	Recommended for previously treated active RRMS, only if alemtuzumab is contraindicated or otherwise unsuitable
Ponesimod	Sphingosine-1-phosphate inhibitor	Oral, once daily	Adult patients with relapsing forms of multiple sclerosis (RMS) with active disease defined by clinical or imaging features.	TA767[42]	Recommended for previously treated active RRMS
Cladribine	Not fully known	Oral, 4-5 days over 2-week treatment courses	Adult patients with highly active relapsing multiple sclerosis (MS) as defined by clinical or imaging features	NICE TA616[38]	Recommended for highly active MS only if the person has rapidly evolving severe RRMS or disease that has responded inadequately to treatment with DMT
Recommended for SPMS					
Siponimod	Sphingosine 1-phosphate	Oral, once daily	Adult patients with secondary progressive multiple sclerosis (SPMS) with active disease evidenced by relapses or imaging	TA656[30]	Recommended as an option for treating SPMS with evidence of active disease

Drug name	Mechanism of Action	Administration route and frequency	Marketing authorisation	Related NICE TA	NICE recommendation
	receptor modulator		features of inflammatory activity.		(that is, relapses or imaging features of inflammatory activity)
Interferon beta-1b (Extavia)	Not fully known	SC injection, every other day	Patients with secondary progressive multiple sclerosis with active disease, evidenced by relapses.	TA527[31]	Recommended for SPMS with continuing relapses
Recommended for PPMS					
Ocrelizumab	Anti-CD20 mAb	IV infusion, every 6 months	Adult patients with early primary progressive multiple sclerosis (PPMS) in terms of disease duration and level of disability, and with imaging features characteristic of inflammatory activity.	TA585[43]	Recommended for treating early PPMS with imaging features characteristic of inflammatory activity
Not recommended					
Interferon beta-1b (Betaferon)	Not fully known	SC injection, every other day	• Patients with a single demyelinating event with an active inflammatory process, if it is severe enough to warrant treatment with intravenous corticosteroids, if alternative diagnoses have been excluded, and if they are determined to be at high risk of developing clinically definite multiple sclerosis. • Patients with relapsing-remitting multiple sclerosis and two or more relapses within the last two years). • Patients with secondary progressive multiple sclerosis with active disease, evidenced by relapses.	TA527[31]	**Not recommended**
Ozanimod	Sphingosine 1-phosphate receptor modulator	Oral, once daily	Adult patients with relapsing remitting multiple sclerosis (RRMS) with active disease as defined by clinical or imaging features	TA706[44]	**Not recommended** for treating active RRMS

2 Decision Problem

Sections of this Chapter have been reproduced from the study's Protocol document, available at the NICE website.[1]

2.1 Technologies and population of interest for this appraisal

The technologies of interest for this appraisal are Natalizumab (Tysabri, Biogen) and natalizumab biosimilar (Tyruko, Sandoz). Natalizumab (Tysabri) has a marketing authorization for subcutaneous and intravenous administration, whereas natalizumab biosimilar (Tyruko) has a license for intravenous administration only. Both drugs have been licensed as single disease modifying therapy (DMT) in adults with highly active relapsing remitting multiple sclerosis for the following people:

- People with rapidly evolving severe RRMS defined by 2 or more disabling relapses in one year, and with 1 or more Gadolinium enhancing lesions on brain Magnetic Resonance Imaging (MRI) or a significant increase in T2 lesion load as compared to a previous recent MRI.

OR

- People with highly active disease despite a full and adequate course of treatment with at least one disease modifying therapy

NICE already recommends natalizumab as a first-line treatment option for people with rapidly evolving severe relapsing–remitting multiple sclerosis (NICE TA127;[34]
Table 3) covering the first part of the population above. This appraisal therefore focuses only **on highly active relapsing-remitting multiple sclerosis after at least one disease modifying therapy**. Table 2 provides a summary of how different subtypes are classified.

2.2 Comparators for this appraisal

The comparator for this appraisal is standard care without natalizumab or natalizumab biosimilar. This includes the following interventions:

- Glatiramer acetate
- Interferon beta 1a
- Interferon beta 1b
- Alemtuzumab
- Cladribine tablets
- Fingolimod
- Ocrelizumab. *The NICE scope*[45] *suggested that this should only be if alemtuzumab is contraindicated. However, our clinical advisors suggested that this is not reflective of this drug is used in clinical practice and so we will not apply this restriction for our appraisal.*
- Ofatumumab
- Ponesimod
- Autologous haematopoietic stem cell transplantation

3 Aim and Objectives

Sections of this Chapter have been reproduced from the study's Protocol document, available at the NICE website.[1]

The overall aim of this assessment was to appraise the clinical and cost effectiveness of natalizumab (Tysabri) and natalizumab biosimilar (Tyruko) within their marketing authorisations for treating highly active RRMS after at least one disease modifying therapy.

To address this aim, we completed the following:

1. Systematic literature review (SLR) of treatments for highly active RRMS after at least one disease modifying therapy
2. Network meta-analysis to estimate the clinical effectiveness and safety of treatments for highly active RRMS after at least one disease modifying therapy
3. Economic modelling to assess the cost-effectiveness of treatments for highly active RRMS after at least one disease modifying therapy

4 Assessment of clinical effectiveness

Sections of this Chapter have been reproduced from the study's Protocol document, available at the NICE website.[1]

We conducted an SLR to summarise the effectiveness of treatments for relapsing-remitting multiple sclerosis after at least one disease modifying therapy. The SLR followed the principles outlined in the Centre for Reviews and Dissemination (CRD) guidance for undertaking reviews in health care and the NICE Health Technology Evaluations Manual.[46, 47] and is reported according to the PRISMA 2020[48] and PRISMA NMA statements.[49]

4.1 Selection criteria

Studies that met the following criteria were eligible for inclusion:

4.1.1 Participants

The population of interest for this appraisal is people with highly active RRMS who have received at least one previous DMT (see Table 3). As we did not expect to find studies for all interventions of interest in this specific sub-population, inclusion for the SLR was broadened to include all studies in patients with RRMS. RRMS was defined broadly to include studies of "relapsing MS". Studies were included if at least 90% of the participants had RRMS or if data could be extracted for this sub-population of interest.

4.1.2 Interventions

The two interventions of interest for this appraisal are **natalizumab** (300 mg IV infusion, every 4 weeks can also be given subcutaneously – referred to as natalizumab IV300 or natalizumab SC) and **natalizumab biosimilar** 300 mg IV infusion, every 4 weeks. To allow comparison with standard care we also included trials that evaluated the treatments summarised in Table 4. This also shows the intervention label used in tables and figures for each of these specific intervention doses.

Table 4 Overview of eligible comparator interventions

Treatment	Dose	Frequency	Admin-istration	Label in tables and figures
Alemtuzumab	12mg	Month 1 - daily for 5 days in month 1; month 12 - daily for 3 days	IV	Alemtuzumab IV12
Autologous haematopoietic stem cell transplantation				AHSCT
Cladribine	3.5 mg/kg	4-5 days over 2-weeks	Oral	Cladribine O3.5
Fingolimod	0.5 mg	once daily	Oral	Fingolimod O0.5
Glatiramer acetate	20 mg	Daily	SC	Glatiramer acetate SC20
Glatiramer acetate	40 mg	Daily	SC	Glatiramer acetate SC40
Interferon beta 1a (avonex)	30 mcg	Weekly	IM	Interferon beta 1a IM30
Interferon beta 1a (rebif)	22 mcg	3 times weekly	SC	Interferon beta 1a SC44
Interferon beta 1a (rebif)	22 mcg	3 times weekly	SC	Interferon beta 1a SC44
Interferon beta 1b	250 mcg	every other day	SC	Interferon beta 1b IM 2 50

Treatment	Dose	Frequency	Admin-istration	Label in tables and figures
Ocrelizumab	600 mg	every 6 months	IV	Ocrelizumab IV600
Ofatumumab	20 mg	every 4 weeks	SC	Ofatumumab SC20
Peginterferon beta 1a	125 mcg	every 2 weeks	SC	Peginterferon beta 1a S C125
Ponesimod	20 mg	Once daily	Oral	Ponesimod O20

SC: subcutaneous; IV: intravenous; IM: intra-muscular

Studies were required to compare one of the interventions above to an alternative intervention listed above, or to placebo, so that only studies that are informative for the network were included. We excluded studies that only compared different doses, modes of administration, or manufacturers of the same intervention unless these were needed to create a connected network.

4.1.3 Outcomes

Studies that report data on any of the following outcomes were eligible for inclusion:

- Relapse rate
- MRI measurements
- Disability progression
- Disease progression
- Adverse effects of treatment
- Health-related quality of life

4.1.4 Study design

We restricted inclusion to randomised controlled trials; open label extension studies were not eligible. No language or publication restrictions were applied.

4.2 Identification of studies

4.2.1 Literature searches

Studies/reports were identified using bibliographic and non-bibliographic search methods following guidance in the NICE technology appraisal manual.[47]

Bibliographic searching

The following databases were searched:

- MEDLINE (Ovid) 1946 to April 30, 2024
- Embase (Ovid) 1974 to 2024 April 30

The search strategy was written by one researcher and checked by another, taking the following form:

1. Terms for relapsing remitting MS
2. Terms for Interventions listed in section 4.1.2

3. The Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity- and precision-maximizing version (2008 revision) supplemented with the Cooper P3 filter[50, 51]
4. 1 and 2 and 3

The bibliographic search strategy was not limited by date of publication or by language. The searches strategies are reported in Appendix 1.

Non-bibliographic search methods

Completed and ongoing trials were identified through searches of the following trials registry resources:

- ClinicalTrials.gov via www.clinicaltrials.gov; and
- World Health Organisation (WHO) International Clinical Trials Registry Platform (ICTRP) via www.who.int/clinical-trials-registry-platform.

For included studies, the study's web page on the trials registry resource was re-checked for data (published results) or linked publications.

Whilst SLRs were not eligible for inclusion, any SLRs published in the last three years (2021-current) and which aligned with our scope, were retained. We checked the studies included in each review to identify any studies not identified by our searches.

NICE requested submissions from Companies with technologies in scope for this appraisal (See Table 3). We checked the submissions for studies (and study data) which align with our inclusion criteria. Any studies identified through this process were tabulated to show where they contributed to our review or why they were excluded (Appendix 2).

4.2.2 Managing the searches

Search results were exported to EndNote 20 for de-duplication. We compared the studies and study reports from the mapping of TAs to our search results. Search results were exported to Microsoft Access for screening.

4.2.3 Studies included in existing TAs

We reviewed existing TAs of interventions or comparators of interest for this appraisal to determine whether they had included any studies that were not identified by our searches. We also reviewed existing TAs for additional data not available in study reports. Where additional relevant data were found, these were included in the review.

4.3 Review strategy

4.3.1 Title and abstract screening

Titles and abstracts from the literature searches were screened independently by two reviewers using a Microsoft Access database developed specifically for this review. At this stage all records that evaluated one of the interventions of interest in the broad population

of patients with RRMS were retrieved. Full copies of all reports considered potentially relevant were obtained and moved to the inclusion assessment stage. Studies included in existing TAs moved straight to the inclusion assessment stage.

4.3.2 Full text inclusion assessment

Full text studies, including all reports included in existing TAs, were assessed for inclusion against the criteria specified in section 4.1. At this stage of the review process, we moved our review management to a new online systematic review management software – Nested Knowledge (www.nested-knowledge.com). One reviewer assessed studies for inclusion. Where studies were excluded, the reason for exclusion was recorded. For included studies, we recorded basic information for each study including language of report, MS population subtype (e.g. RRMS, SPMS, PPMS, other, mixed), whether data were available for the highly active RRMS sub-population, interventions evaluated, whether outcomes of interest were reported, study design, and study name or trial registry ID. Inclusion assessment and recorded information was checked by a second reviewer. Any disagreements were resolved by consensus or discussion with a third reviewer.

4.3.3 Mapping reports to studies

All reports of studies that met the review inclusion criteria progressed to the mapping stage. This stage linked multiple reports of the same study. The information recorded at the inclusion assessment stage was used to help identify linked reports. We identified a "primary report" for each study, this was the study that reported the most complete trial data and results. Other reports, including NICE technology appraisals that included the primary report, were labelled as secondary reports and were linked within Nested Knowledge. For each linked report we recorded whether data were extracted from the report, and if so, what data were extracted.

4.3.4 Data extraction

Data were extracted using standardised data extraction forms developed in Nested Knowledge (www.nested-knowledge.com). Data extraction forms were piloted on a small sample of papers and adapted as necessary. Data were extracted by one reviewer and checked in detail by a second reviewer. Any disagreements were resolved by consensus or discussion with a third reviewer. Nested knowledge offers some artificial intelligence (AI) features that we used to support data extraction of some baseline data. It incorporates a feature known as "smart tag" recommendations that uses GPT 4, a large language model from OpenAI, to provide automatic highlighting of full texts based on our configured "tags" (fields to extract data to). This was not used to replace human reviewers but as a tool to streamline the data extraction process. Both reviewers read the full text and relevant supplementary materials of all included studies in detail to identify and extract relevant data.

Baseline data

Data were extracted on the following:

- Study phase
- Funding sources (public, industry, mixed)
- Full text or conference abstract
- NCT number
- Study location
- Population
    - Criteria used to diagnose MS
    - Proportion of participants with RRMS
    - RRMS subtype
    - Previous treatment
- Interventions
    - Treatment names
    - Mode of administration
    - Dose
    - Frequency
- Number of participants (eligible, randomised and treated)
- Age
- Sex
- Ethnicity
- EDSS score
- Time from diagnosis of MS to study entry
- Annual relapse rate at baseline

For continuous measures, we extracted mean and standard deviation (SD) in each intervention group – this was reported by the majority of studies. If standard error (SE) was reported instead of the SD, we extracted the SE and sample size (n) and used this to calculate the SD by multiplying the SE by √n. If the SD and SE were not reported we extracted the range or interquartile range, where reported.

If the mean relapse rate was reported over a time period of different than one year, we calculated the mean annual relapse rate by dividing the reported relapse rate by the time period over which the relapse rate was calculated.

Outcome data

Where possible results data were extracted for both the sub-population of interest (highly active RRMS) and for the overall RRMS population. Data were extracted for the time points closest to 12, 24 and 36 months follow-up reported in each study. Where data were only reported graphically, data were extracted from the graphs where possible.

Annualised relapse rate

Studies used different definitions of a relapse, where reported we extracted data on the definition used in each study. We extracted the most appropriate data reported in each

study to calculate the annual relapse rate ratio and 95% confidence interval, based on the following hierarchy:

I. Rate ratios (RR) together with 95% CIs and p-values for comparisons between groups together with details on the methods of analysis, any variables controlled for in the analysis and the test statistic. The reported rate ratios for ARR were converted to the log rate ratio scale (i.e. a log link). The standard error for the log rate ratio was calculated by assuming normality on the log scale and assuming the upper and lower 95% confidence intervals are separated by $2 \times 1.96 \times SE$. If the log rate ratio of an event on arm k relative to arm 1 in trial i is denoted y_{ik} and its standard error se_{ik} ($k \geq 2$) we use the Normal likelihood

$$y_{ik} \sim N(\theta_{ik}, se_{ik}^2)$$

Using the identity link the linear predictor is

$$\theta_{ik} = \delta_{ik}$$

II. Annual relapse rate in each intervention group, together with 95% CIs and p-value for comparisons between groups. For such studies we therefore modeled the absolute log hazard rate for CDP3/6 or log rate for ARR for each arm h_{ik} with standard error hse_{ik}^2, again calculated using $2 \times 1.96 \times SE$, as

$$h_{ik} \sim N(\theta_{ik}, hse_{ik}^2)$$

With link function

$$\theta_{ik} = \mu_i + \delta_{i,bk} I_{k \neq 1}$$

Where μ_i represents the log rate on baseline arm $k = 1$.

III. Annual relapse rate in each intervention group together with number of events per arm for comparisons between groups, together with details on the methods of analysis, any variables controlled for in the analysis and the test statistic.
For these studies we used use rates to calculate rate ratio and SE(lnRR) (using rate and number of participants to calculate number of events), as follows,[52] where E represents the number of events:

$$RR = \frac{ARR_1}{ARR_2}$$

$$SE = \sqrt{\frac{1}{E_1} + \frac{1}{E_2}}$$

The calculated rate ratios were also converted to the log rate ratio scale as shown in I.

Disability progression

We extracted data on:

- 3 months confirmed disability progression (CDP3)
- 6 months confirmed disability progression at (CDP6)

These outcomes refer to the proportion of participants who have confirmed disability progression based on their EDSS scores sustained for at least 3 (CDP3) or 6 months (CDP6). Disability progression is usually defined as an increase in EDSS by ⩾1.0 point from the baseline EDSS if the baseline EDSS is ⩽5.5 or an increase of ⩾0.5 points if the baseline EDSS is >5.5.[53] However, studies may use different definitions and so we also extracted the exact definition used in each study.

We extracted data on the following, where reported:

- Hazard ratios for time to CDP3 and time to CDP6 together with 95% CIs and p-values
- Proportion of participants with CDP3 and CPD6.

Reported HRs were treated in the same way as RRs for ARR, as shown in I. When HRs were not reported they were estimated with a hazard rate analysis of event frequencies in relation to time at risk (when follow-up time was available), or from 2x2 tables of event numbers using complementary log-log (cloglog) transformations, assuming proportional hazards,[52] using

$$HR = \frac{E_2 T_1}{E_1 2}$$

Where E is number of events and T is persons-years at risk, and we estimated the SE of the log hazard rate or log rate using[54]

$$SE = \sqrt{\frac{1}{E_1} + \frac{1}{E_2}}$$

Calculated HRs were treated in the same way as calculated RRs for ARR.

MRI outcomes

We only extracted data on the following MRI outcomes, where reported:

- Proportion of participants with gadolinium enhancing (gd+) T1 lesions. We were primarily interested in the total number of lesions.
- Proportion of participants with T2 lesions. We were primarily interested in the those with new or enhancing T2 lesions.

Studies reported slightly different definitions of gd+ lesions and new or enlarging T2 lesions – we extracted details on how these were defined in each study.

We used data on the proportion of participants with lesions in each intervention group and follow-up time to calculate hazard ratios in the same way as it was done for disability progression.

Adverse events

We extracted data on the proportion of participants in each intervention group that experienced the following categories of adverse events (AEs):

- Any AEs
- Treatment related AEs
- Discontinuation due to AEs
- Serious AEs
- Grade 3 or 4 AEs

We used data on the proportion of participants with each type of AEs in each intervention group and follow-up time to calculate hazard ratios in the same way it was done for disability progression. For zero count cells, a continuity correction was applied where a constant (0.5) was added to each cell of the 2x2 table.

We also extracted data on the AEs reported, but did not record the number of participants with each specific AE.

Health-related quality of life

We only extracted data on quality of life measured using the EuroQol 5 dimensions (EQ-5D) or Self-Reported SF-36 scales, but also noted where data were available for other scales. We extracted means/medians together with ranges, standard deviations (SD), standard errors (SE) and/or confidence intervals (CIs) at baseline and follow-up. Summary effect estimates (e.g. mean difference (MD)) together with 95% CIs and p-values for comparisons were extracted.

4.3.5 Quality assessment strategy

The methodological quality of included RCTs was assessed using the updated Cochrane Risk of Bias Tool (RoB-2).[55] This considers the risk of bias across five domains: randomisation process, deviations from the intended interventions, missing outcome data, measurement of the outcome and selection of the reported result. Domains are rated as “low risk of bias”, “high risk of bias” or “some concerns”. An overall risk of bias assessment is generated based on the “worst” risk of bias in any individual domain i.e. if one domain is judged at high risk of bias the whole study is considered at high risk of bias. Risk of bias assessment was done at the outcome level for the outcomes of ARR, disease progression, MRI outcomes and safety outcomes. Any disagreements were resolved by consensus or discussion with a third reviewer.

4.3.6 Methods of data synthesis

For each population and outcome, we present a narrative summary of included studies. This includes a summary of study characteristics (e.g. sample size, geographical location, publication year) and baseline participant characteristics (proportion of participants that did not have RRMS, age, sex, ethnicity, EDSS scores, annual relapse rate, disease duration, proportion of patients who had received previous DMT treatment) and risk of bias.

Network Meta-Analysis

To compare the efficacy and safety of treatment options using the available trial information, Bayesian Network Meta-Analyses (NMA) was conducted. NMA strengthens inference concerning the relative effect of two treatments by including both direct and indirect comparisons while respecting randomisation. Most treatments were not compared in head-to-head RCTs, and NMA allowed for the use of indirect information to make such comparisons. General details of NMA are given in NICE Decision Support Unit Technical Support Document 2.[56] Interventions with different doses were considered as separate nodes. An exception was made for the analysis for the HARRMS population, where beta-interferons 1a were grouped to create a single node to allow the network to connect. This is similar to the approach of TA767 on posenimod.[42] Table 5 provides an overview of each intervention included in the NMA.

Random and fixed effects analyses were performed. For the random-effects models the trial-specific log ratios come from a normal distribution with an estimated heterogeneity variance which is assumed to be the same for all treatment comparisons. For the fixed-effects model the log ratios were assumed to be the same across studies, which is equivalent to setting the between-trial heterogeneity to zero thus assuming homogeneity of the underlying true treatment effects.

Vague priors (Fixed effects model: prior_intercept = normal (0, scale = 10), prior_trt = normal (0, scale = 10), random effects model: prior_intercept = normal (0, scale = 10), prior_trt = normal (0, scale = 10), prior_het = half_normal (scale =2), adapt_delta = 0.99) were used for Bayesian estimation of all treatment effect parameters and for the heterogeneity variance in random effects models, unless the model presented convergence issues. In these cases, informative priors were used and reported together with results in Appendix 4.[57, 58]

Model assessment and selection

Model selection between fixed and random effects was based on the Deviance Information Criterion (DIC), with a difference of 3-5 points considered meaningful.[59, 60] For models with similar DIC we selected the simplest model (lowest effective number of parameters) as this supports interpretability. The total residual deviance, as described in NICE DSU TSD 2,[56] was calculated, and compared to the number of datapoints as an overall assessment of goodness-of-fit.[56] Studies with high residual deviance were qualitatively assessed (e.g., for differences in line of therapy, disease severity, year of publication, concomitant medications).

Network meta-regression

NMA assumes that all effect modifiers are balanced across studies both within (homogeneity) and between (consistency) treatment comparisons. We had intended to assess the impact of effect modifiers using aggregate data network meta-regression, as described in NICE DSU TSD 3[61] for the outcomes ARR and disease progression. However, as

there was little evidence of heterogeneity for ARR and CDP3, and insufficient studies for CDP6, meta-regression was not conducted. Instead, we conducted a sensitivity analysis restricted to studies judged at low risk of bias for ARR, the only outcome with sufficient studies for this to be considered appropriate.

Inconsistency testing

For any networks of evidence with closed loops of direct and indirect evidence we assessed consistency in the final by conducting a node-splitting analysis. Node-splitting models were fitted, where each comparison in the network was split into its direct and indirect components. For each node, we compared the estimates derived from direct and indirect evidence for comparisons against placebo, by calculating the difference in treatment effects and assessing whether the 95% credible intervals (CrIs) overlapped. We also examined the Bayesian p-values from the node-splitting models, which indicate whether there is evidence of inconsistency (i.e., significant differences between direct and indirect evidence).[62]

Model Implementation

Data preparation was conducted in the R programming language.[63] The NMA models were fitted in a Bayesian framework using the R package 'multinma'.[60, 64] Sufficient chains and Markov Chain Monte Carlo (MCMC) samples were used for burn-in and sampling. Convergence was assessed by visual inspection of the trace plots and the Brookes-Gelman-Rubin (BGR) Rhat statistic, which is reported for model parameters.[60]

Populations

We conducted our NMA on all feasible outcomes in the following populations:

1. HARRMS (or studies with at least 90% participants in this group)
2. Any RRMS, including studies with at least 90% of participants with RRMS.

A sensitivity analysis was conducted where a restricted NMA was created for population 2, including only interventions assessed in population 1.

Timepoints

Studies reported outcomes at multiple timepoints. We included all reported time points in the analysis, where studies reported outcomes at multiple time-points we selected the longest follow-up period. Where appropriate data were available, we used hazard ratios to account for differing follow-up periods across the included studies. We had intended to conduct a sensitivity analysis where we would have conducted separate analyses for 12, 24 and 36 months follow-up. However, there were insufficient data on time-points other than 24 months and so this analysis was not considered feasible.

Handling of multi-arm trials

Multi-arm trials were included in the network meta-analysis, and all relevant arms were included in the analyses. These studies were handled automatically using the multinma package in R, which adjusts for correlations within multi-arm studies.

Summary of results

Results were summarised as the mean of the posterior distribution of the treatment effect. The results of the NMA were presented in terms of cross tables with relative treatment effect estimates between all interventions of interest with 95% CrI for all outcomes presented. We also plotted data, including results from the node split models on forest plots to show effects of each intervention included in the network relative to placebo. All results are reported with 95% credible intervals (CrI). The 95% CrI were calculated as the lower 2.5th and upper 97.5th percentile of the MCMC samples. One of the advantages of NMA is that it allows for the ranking of interventions. Based on the results of the NMA, we calculated the probability of each treatment is ranked 1st best, 2nd best, etc. We also presented the mean ranking for each intervention together with 95% CrI, and league tables (RR of HR with 95% CrI) to show comparisons between each pair of included interventions.

The results of the NMA were also used to inform the economic model, as described in Section 6.5.1.

4.4 Protocol changes

The following changes were made to the protocol. These were either to clarify issues that were ambiguous in the original protocol or to focus the review to make this manageable within the resources and time available. Restrictions to outcomes were discussed with and approved by NICE.

4.4.1 Inclusion criteria:

Population: We clarified that RRMS was defined broadly to include studies of patients reported to have “relapsing MS”, and that we were only interested in studies in adults (>18 year olds).

Interventions: We restricted inclusion to studies that evaluated the interventions of interest at modes of administration and doses licensed for use in UK unless they were required to create a connected network.

Outcomes: Due to time and resource constraints, we restricted inclusion to studies that reported on at least one of the following outcomes:

- Relapse rate
- MRI measurements
- Disability progression
- Disease progression
- Adverse effects of treatment

- Health-related quality of life measured using EQ-5D or SF-36

This means that we did not consider the following outcomes:

- Severity of relapses
- Symptoms of multiple sclerosis (such as fatigue, cognition, and visual disturbance)

4.4.2 Literature searches

Rather than screening the existing TAs as a first step, we screened these after we had completed the data extraction for studies identified by bibliographic and non-bibliographic search methods. This was a logistical change to allow us to also determine whether there were any additional data reported in the TAs that were not available in reports of the studies. Additional data could then be included in the review.

4.4.3 Data extraction

We restricted data extraction to the outcomes listed above, focusing specifically on those listed in the methods section of the report. Data extraction was performed in Nested Knowledge instead of Access as initially proposed. We were not aware of this programme at the time the protocol was written – this allowed two reviewers to work remotely on the same database and provided greater efficiencies in the review process.

Due to time and resource constraints, we restricted data extraction and synthesis to the outcomes:

- Annualised Relapse Rate (ARR)
- Disease progression (CDP3 and CDP6)
- MRI outcomes (proportion of participants with Gd+ or new or enhancing T2 lesions)
- Adverse events (any AEs, serious AEs, grade 3-4 AEs, treatment related AEs and discontinuation due to AEs)
- Quality of life

4.4.4 Synthesis and network meta-analysis

Dichotomous data (proportion of participants with MRI lesion sand AE outcomes) were analysed as time to event outcomes, with HR and se(logHR) calculated as shown in 4.3.4. This was done because all outcomes were only expected to occur once per patient, and it allowed us to introduce follow-up time into our calculations.

We had planned to use network meta-regression to investigate heterogeneity in relapse rates and disease progression across studies. However this was not considered to be appropriate for ARR as there was little evidence of heterogeneity, and there were not enough data for other outcomes.

Consistency was evaluated using node splitting and plotting indirect and direct effect estimates against NMA results. Bayesian p-values were also considered. We did not find any inconsistencies, so a comparison of model fit with the Unrelated Mean Effects (UME) model was not done.

We removed the prediction of absolute outcomes from the NMA as absolute outcomes in data from the MS Registry analysis was available to inform the economic model.
We had intended to conduct a sensitivity analysis for the HARRMS population, where treatments that were disconnected would be included through an “any RRMS” study from population 2. Instead, we conducted a sensitivity analysis where a restricted NMA was created for the general RRMS population, including only interventions assessed in people with HARRMS. This restricted NMA in the general RRMA population was plotted together with results from the equivalent network in the HARRM population for comparison. We considered that this would provide a better comparison of whether interventions are similarly effective in the RRMS and HARRMS populations.

5 Results of clinical effectiveness review

Our searches identified 3021 records of which 701 reports were considered potentially relevant after screening titles and abstracts and were retrieved for full text review. We identified two additional relevant studies – one that was published since the searches[65] but for which the trial registry entry was identified by the searches, and one abstract included in a previous systematic review. We were unable to locate a full report of this study and the abstract did not contain sufficient details to include the trial.[66] The flow of studies through the review process is shown in the PRISMA flow diagram in Figure 2.[48]

We included 42 studies (22, 409 participants) reported in 178 reports. This includes two sets of paired studies (OPERA I and OPERA II[67] and ASCLEPIOS I and II[68]) that were reported together in the same set of reports. Table 43 (Appendix 3) provides an overview of each included study,
Table 44 (Appendix 3) summarises reports related to each study and whether additional data were extracted from each report. Studies excluded at the full text assessment stage are summarised in Table 41 (Appendix 2), together with reasons for exclusion. The submissions from the manufacturers for the two drugs of interest for this appraisal (Biogen and Sandos) did not include any relevant studies that we had not identified in our searches – studies included in these submissions, review decision, and reasons for exclusion (where appropriate) are summarised in Table 39 and Table 40 (Appendix 3). We identified a further eight studies that appeared to meet inclusion criteria but are currently ongoing and so results are not yet available. These are summarised in Table 38 (Appendix 2) – interventions being evaluated include stem cell transplantation (4 studies), ocrelizumab, ofatumumab, interferon beta-1a, interferon beta-1b, glatiramer acetate and natalizumab (each in single studies) .

We only identified one small study ofatumumab - APOLITOS[69], and this was conducted in the very specific population of Japanese and Russian participants. We therefore expanded our inclusion criteria to include studies that compared ofatumumab to other interventions not specified in our original inclusion criteria. This lead to the inclusion of an additional 2 studies: ASCLEOPIO I and II[68] that compared ofatumumab to teriflunomide. To create a connected network, we also included the OPTIMUM trial[70] that compared teriflunomide with ponesimod. These three studies are included in our total number of 42 included studies.

Two of the 42 studies included in our review – CARE-MS II[71] and MIST[72] - were restricted to participants with HARRMS. All other studies reported data for the full RRMS population. Six studies (CLARITY[73], FREEDOMS[74], FREEDOMS II[73], OPERA I and II[67], and TRANSFORMS)[75] also reported additional data for a subset of patients with HARRMS. There were no data on natalizumab or natalizumab biosimilar in people with HARRMS.

Table 5 provides an overview of the interventions evaluated by the included studies – different doses of the same interventions were considered as separate interventions.

Twenty studies included a placebo control group, three of these also included an active comparator, and 22 studies included active comparators only. We identified only one study of AHSCT, the MIST study.[76] This study was conducted in patients with HARRMS and compared AHSCT to a DMT. Patients in the DMT group received a DMT of higher efficacy or a different class to the intervention they had been taking at the time of randomisation, based on the judgement of the neurologist - this meant that individual patients received different DMTs.

Only four studies evaluated natalizumab or natalizumab biosimilar, the technologies of interest for this appraisal - ANTELOPE[76], AFFIRM[77], REVEAL[78] and Saida 2017[79]. AFFIRM and Saida 2017 compared natalizumab to placebo, REVEAL compared natalizumab to Fingolimod, and ANTELOPE compared natalizumab to natalizumab biosimilar. All studies of natalizumab evaluated intravenous administration; there were no studies that fulfilled our inclusion criteria of subcutaneous administration. Table 6 provides an overview of the four studies that evaluated natalizumab. All four studies used the McDonald criteria to diagnose MS and were industry funded. Saida 2017 was conducted in Japanese patients, REVEAL did not report on ethnicity but was conducted across 9 countries, and in AFFIRM and ANTELOPE most participants (94-100%) were white. AFFIRM had a follow-up duration of 24 months, follow-up duration was short (24-52 weeks) in the other three studies. A large proportion of patients in the Saida 2017 study had received previous DMT treatment (88%), and participants were required to have had at least one relapse at baseline, meaning participants were close to fulfilling our definition of HARRMS. Half of participants had received previous DMT treatment in REVEAL, while only 9% of those in AFFIRM had received treatment; information on previous treatment was not reported for ANTELOPE. All studies reported on relapse rates and AEs, and all but Saida 2017 reported in the proportion of participant with MRI lesions. AFFIRM was the only study to provide data on disease progression.

Figure 2 PRISMA Flow diagram

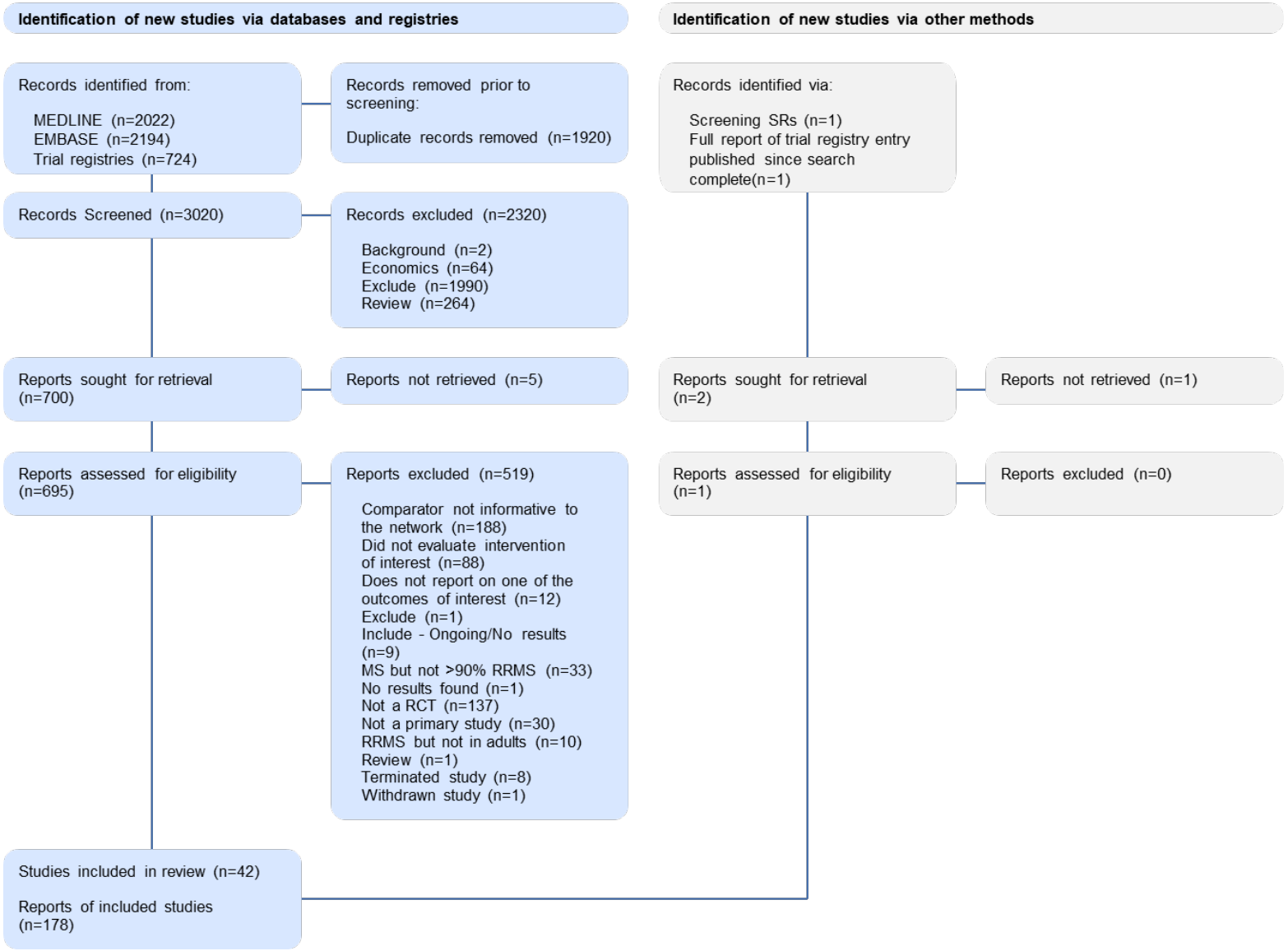


Table 5 Overview of interventions evaluated in each of the included studies

Study Name	Population	Intervention																		
		Placebo	Interferon beta 1a IM30	Interferon beta 1a SC44	Interferon beta 1a SC22	Interferon beta 1b SC250	Peginterferon beta 1a SC125	Glatiramer acetate SC20	Glatiramer acetate S420	Fingolimod O0.5	Ponesimod O20	Ocrelizumab IV600	Alemtuzumab IV12	Natalizumab IV300	Natalizumab biosimilar	Ofatumumab SC20	Cladribine O3.5	Teriflunomide O14	AHSCT
ADVANCE[80]	RRMS	x					x												
AFFIRM[77]	RRMS	x												x					
ANTELOPE[76]	RRMS													x	x				
APOLITOS[69]	RRMS	x														x			
ASCLEPIOS I[68]	RRMS															x		x	
ASCLEPIOS II[68]	RRMS															x		x	
ASSESS[81]	RRMS							x		x									
BEYOND[82]	RRMS					x		x											
Calabrese 2012[83]	RRMS	x		x				x											
CAMMS223[84]	RRMS			x									x						
CARE-MS I[85]	RRMS			x									x						
CARE-MS II[71]	HA			x									x						
CLARITY[86]	RRMS + HA		x														x		
CombiRx[87]	RRMS		x					x											
CONFIDENCE[88]	RRMS							x	x										
CONFIRM[89]	RRMS	x						x											
Copolymer 1 Multiple Sclerosis Study Group[90]	RRMS	x						x											
Etemedifar 2006[91]	RRMS		x	x		x													
European/ Canadian	RRMS	x						x											

Study Name	Population	Intervention																		
		Placebo	Interferon beta 1a IM30	Interferon beta 1a SC44	Interferon beta 1a SC22	Interferon beta 1b SC250	Peginterferon beta 1a SC125	Glatiramer acetate SC20	Glatiramer acetate S420	Fingolimod O0.5	Ponesimod O20	Ocrelizumab IV600	Alemtuzumab IV12	Natalizumab IV300	Natalizumab biosimilar	Ofatumumab SC20	Cladribine O3.5	Teriflunomide O14	AHSCT
glatiramer acetate study group[92]																			
EVIDENCE[93]	RRMS		x	x															
FREEDOMS[74]	RRMS + HA	x								x									
FREEDOMS II[73]	RRMS + HA	x								x									
GALA[94]	RRMS	x							x										
GATE[95]	RRMS	x						x											
GOLDEN[96]	RRMS					x				x									
IFNB Multiple Sclerosis Study Group[97]	RRMS	x				x													
IMPROVE[98]	RRMS	x		x															
INCOMIN[99]	RRMS		x			x													
Kappos 2011[100]	RRMS	x	x									x							
MIST[72]	HA																		x
OPERA I[67]	RRMS + HA			x								x							
OPERA II[67]	RRMS + HA			x								x							
OPTIMUM[70]	RRMS										x							x	
PEGINTEGRITY[65]	RRMS	x					x												
Ponesimod Phase II study Group[101]	RRMS	x									x								
PRISMS[102]	RRMS	x		x	x														
REGARD[103]	RRMS			x				x											
REVEAL[78]	RRMS									x				x					

Study Name	Population	Intervention																		
		Placebo	Interferon beta 1a IM30	Interferon beta 1a SC44	Interferon beta 1a SC22	Interferon beta 1b SC250	Peginterferon beta 1a SC125	Glatiramer acetate SC20	Glatiramer acetate S420	Fingolimod O0.5	Ponesimod O20	Ocrelizumab IV600	Alemtuzumab IV12	Natalizumab IV300	Natalizumab biosimilar	Ofatumumab SC20	Cladribine O3.5	Teriflunomide O14	AHSCT
Saida 2012[104]	RRMS	x								x										
Saida 2017[79]	RRMS	x												x						
The Multiple Sclerosis Collaborative Research Group	RRMS	x	x																	
TRANSFORMS[75]	RRMS + HA		x							x										

RRMS: Relapsing remitting MS; HA: highly active

Table 6 Overview of study details and baseline characteristics for studies that evaluated natalizumab or its biosimilar

Study Name	Interventions evaluated	Number enrolled	Duration (median follow-up)	Study Location	Age	% Female	Years from diagnosis	EDSS	Relapse rate	% treated	Outcomes reported
AFFIRM[77]	Natalizumab Placebo	943	2 years	99 sites in Europe, North America, and New Zealand	36.0	70	NR	2.3	1.5	9	ARR, CDP3, CDP6, MRI Gd+, MRI T2, any AEs, SAEs, AEs leading to treatment discontinuation
ANTELOPE[76]	Natalizumab Natalizumab biosimilar	265	48 weeks	48 sites in 7 countries	36.7	61	5.3	3.3	1.4	NR	ARR, MRI Gd+, MRI T2, any AEs, treatment related AEs, AEs leading to treatment discontinuation
REVEAL[78]	Natalizumab Fingolimod O0.5	111	52 weeks	43 sites in nine countries.	36.6	69	4.8	NR	1.9	50	ARR, MRI Gd+, MRI T2, SAEs, treatment related AEs, AEs leading to treatment discontinuation
Saida 2017[79]	Natalizumab Placebo	94	24 weeks	25 sites in Japan	36.4	70	5.5	2.2	2.0	88	ARR, any AEs, SAEs, AEs leading to treatment discontinuation

Table 7 Risk of bias for studies in the general RRMS population

Study	Outcome	Domain					Overall	Rationale
		1	2	3	4	5		
ADVANCE[80]	ARR; CDP; AE; QoL	Low	Low	Low	Low	Low	**Low**	No concerns for any domains
AFFIRM[77]	ARR; MRI	Low	Low	Low	Low	Low	**Low**	No concerns for any domains; protocol not available but ARR and MRI specified as outcomes in trial registry entry
	CDP					Some concerns	**Some concerns**	Outcome not specified in trial registry entry
	QoL			High		Low	**High**	Outcome data only available for 85% participants
ANTELOPE[76]	ARR; MRI; AE	Low	Low	Low	Low	Low	**Low**	No concerns for any domains
APOLITOS[69]	ARR; AE	Some concerns	Low	Low	Low	Low	**Some concerns**	Insufficient information on randomisation and allocation concealment; no evidence of baseline imbalance; protocol not available
ASCLEPIOS I[68]	ARR; CDP; AE	Low	Low	Low	Low	Low	**Low**	No concerns for any domains
ASCLEPIOS II[68]	ARR; CDP; AE	Low	Low	Low	Low	Low	**Low**	No concerns for any domains
ASSESS[81]	ARR; MRI; AE	Low	High	High	Low	Low	**High**	Patients and carers were aware of the treatment assignments; large proportion of withdrawals potentially related to outcomes; subset received MRI; all participants included in analysis, but details on ITT analysis lacking
BEYOND[82]	ARR; CDP; AE	Low	Low	Low	Low	Some concerns	**Some concerns**	Protocol not available
Calabrese 2012[83]	ARR	Some concerns	Some concerns	Low	Some concerns	Some concerns	**Some concerns**	Insufficient information on allocation concealment; no evidence of baseline imbalance; patients and carers were aware of the treatment assignments but no evidence of protocol deviations because of trial context; no information on blinding of outcome assessors; protocol not available
CAMMS223[84]	ARR; CDP	Some concerns	Some concerns	High	Low	Low	**High**	Insufficient information on allocation concealment; patients and carers aware of treatment assignment but deviations from intended intervention low; large proportion of missing data potentially related to outcome - all participants included in analysis but details on ITT analysis lacking

Study	Outcome	Domain					Overall	Rationale
		1	2	3	4	5		
	AE			Low				Outcome data available for most participants
CARE-MS I[85]	ARR; CDP; MRI; AE; QoL	Some concerns	High	Low	Low	Low	**High**	Insufficient information on allocation concealment; patients and carers were aware of the treatment assignments
CLARITY[86]	ARR; CDP; MRI; QoL	Low	Low	High	Low	Low	**High**	Over 10% of participants did not complete study & only subset of these had MRI data; missingness could depend on true value. Only 80% of participants had data for QoL
	AEs	Low	Low	Low	Low	Low	**Low**	Data available for all participants
CombiRx[87]	ARR; AE	Low	Low	Low	Low	Low	**Low**	No concerns for any domains
	MRI			Some concerns			**Some concerns**	MRI data only available for subset of patients, unclear how selected; no sensitivity analysis and missingness could depend on true value
CONFIDENCE[88]	AE	Some concerns	Low	Low	High	Some concerns	**High**	Insufficient information on randomisation and allocation concealments; outcome assessors unblinded; no protocol
CONFIRM[89]	ARR; CDP; QoL (except VAS)	Low	Low	Some concerns	Low	Low	**Some concerns**	Data missing for 20% of participants but sensitivity analysis suggest that this did not impact results; protocol not available
	AE; QoL (VAS)			Low			**Low**	AE data for all participants; QoL VAS for >90%
Copolymer 1 Multiple Sclerosis Study Group[90]	ARR; CDP; AE	Some concerns	Low	Low	Low	Some concerns	**Some concerns**	Insufficient information on allocation concealment; no evidence of baseline imbalance; protocol not available
Etemedifar 2006[91]	ARR	Some concerns	Some concerns	Low	Low	Some concerns	**Some concerns**	Insufficient information on allocation concealment; no evidence of baseline imbalance; patients and carers were aware of the treatment assignments but no evidence of protocol deviations because of trial context; protocol not available
European/ Canadian glatiramer acetate study group[92]	ARR; AE	Some concerns	Low	Low	Low	Low	**Some concerns**	Insufficient information on allocation concealment; no evidence of baseline imbalance

Study	Outcome	Domain					Overall	Rationale
		1	2	3	4	5		
EVIDENCE[93]	ARR; CDP; MRI; AE	Low	Some concerns	Low	Low	Some concerns	**Some concerns**	Patients and carers were aware of the treatment assignments but no evidence of protocol deviations because of trial context; protocol not available
FREEDOMS[74]	ARR; CDP; AE	Low	Low	Low	Low	Low	**Low**	No concerns for any domains
	MRI			Some concerns			**Some concerns**	MRI data only available for subset of patients, unclear how selected; no sensitivity analysis and missingness could depend on true value
FREEDOMS II[73]	ARR; CDP; MRI; QoL	Low	Low	High	Low	Low	**High**	Over 25% of participants did not complete study & only subset of these had MRI data; missingness could depend on true value
	AE			Low			**Low**	AE data available for all participants
GALA[94]	ARR; AE	Low	Low	Low	Low	Low	**Low**	No concerns for any domains
GATE[95]	ARR; MRI; AE	Low	Low	Low	Low	Low	**Low**	No concerns for any domains
GOLDEN[96]	ARR	Some concerns	High	High	Low	Some concerns	**High**	Insufficient information on allocation concealment; patients and carers were aware of the treatment assignments; large proportion of missing data potentially related to outcome; protocol not available
	AE			Low				Safety data available for all participants
IMPROVE[98]	ARR; MRI; AE	Some concerns	Some concerns	Low	Low	Some concerns	**Some concerns**	Insufficient information on allocation concealment; no evidence of baseline imbalance; patients and carers were aware of the treatment assignments but no evidence of protocol deviations because of trial context; protocol not available
INCOMIN[99]	ARR; CDP;	Low	High	Low	High	Some concerns	**High**	Patients and carers were aware of the treatment assignments; outcome assessors unblinded; no protocol available
	MRI		Some concerns				**High**	MRI outcome data only available for 80% of participants
IFNB Multiple Sclerosis Study Group[97]	ARR; AE	Some concerns	Low	Low	Low	Some concerns	**Some concerns**	Insufficient information on randomisation and allocation concealment; no evidence of baseline imbalance

Study	Outcome	Domain					Overall	Rationale
		1	2	3	4	5		
Kappos 2011[100]		Low	Low	Low	Low	Low	**Low**	No concerns for any domains
Multiple Sclerosis Collaborative Research Group[105]	ARR; CDP; AE	Some concerns	Low	Low	Low	Low	**Some concerns**	Insufficient information on allocation concealment; no evidence of baseline imbalance
	MRI			Some concerns				MRI data available for 85% of participants
OPERA I[67]	ARR; CDP; MRI; AE; QoL	Low	Low	Low	Low	Low	**Low**	No concerns for any domains
OPERA II[67]	ARR; CDP; MRI; AE; QoL	Low	Low	Low	Low	Low	**Low**	No concerns for any domains
OPTIMUM[70]	ARR; CDP; AE	Low	Low	Low	Low	Low	**Low**	No concerns for any domains
PEGINTEGRITY[65]	ARR; CDP;	Some concerns	High	High	Some concerns	Low	**High**	Insufficient information on allocation concealment and blinding of outcome assessors; patients and carers were aware of the treatment assignments; large proportion of missing data potentially related to outcome
	AE			Low				AE data available for >95% participants
Ponesimod Phase II study Group[101]	ARR; AE	Low	Low	Low	Low	Low	**Low**	No concerns for any domains
PRISMS[102]	ARR; CDP; MRI	Low	Low	Low	Low	Some concerns	**Some concerns**	Protocol not available
REGARD[103]	ARR; CDP; MRI; AE	Low	Low	Low	Low	Some concerns	**Some concerns**	Protocol not available.
REVEAL[78]	ARR; AE	Some concerns	Low	Low	Some concerns	Some concerns	**Some concerns**	Insufficient information on allocation concealment; no evidence of baseline imbalance; no information on blinding of outcome assessors; protocol not available
	MRI			Some concerns				MRI outcomes available for <90% of participants
Saida 2012[104]	ARR; AE	Low	Low	Low	Low	Low	**Low**	No concerns for any domains

Study	Outcome	Domain					Overall	Rationale
		1	2	3	4	5		
	MRI			Some concerns			**Some concerns**	MRI outcome data only available for 88% of participants
Saida 2017[79]	ARR; AE	Low	Low	Low	Low	Low	**Low**	No concerns for any domains
TRANSFORMS[75]	ARR; CDP; AE	Low	Low	Low	Low	Low	**Low**	No concerns for any domains
	MRI			Some concerns				MRI data available for 85% participants

Domain 1: Risk of bias arising from the randomization process; Domain 2: Risk of bias due to deviations from the intended interventions; Domain 3: Risk of bias due to missing outcome data; Domain 4: Risk of bias in measurement of the outcome; Domain 5: Risk of bias in selection of the reported result

ARR: annualised relapse rate; CDP: confirmed disease progression; AE: adverse event; QoL: Quality of Life

5.1 General RRMS population

Forty studies (21 671 participants) reported data for a general RRMS population.

Table 45 (Appendix 3) provides a summary of the baseline characteristics of participants included in the RRMS studies. All studies were considered to be sufficiently similar for inclusion in the NMAs. AHSCT was the only intervention not evaluated in the general RRMS population – this was only evaluated in the HARRMS population. Four studies included a small proportion of participants that did not have RRMS – in ASCLEPIOS I and II 6% of participants had SPMS, in OPTIMUM 3% had SPMS, and in Saida 2012 2% had SPMS. Mean age ranged from 30 to 41 years (median 36.7 years), the proportion of female participants ranged from 31 to 91% (median 68%), baseline EDSS score from 1.0 to 3.5 (median 2.4), baseline annual relapse rate ranged from 0.7 to 2.4 (median 1.5), and mean disease duration at baseline ranged from 0.3 to 8 years (median 5.7 years). The proportion of participants who had received previous treatment with a DMT ranged from 0 to 91% (median 30%). The majority of participants were white (median 92%) although the proportion ranged from 0 to 100% - this is because one study (Saida 2007[79]) was conducted only in Japanese patients and the APOLITOS study[69] was conducted in Japan and Russia. Publication years spanned almost 30 years ranging from 1993 for the earliest study of interferon beta-1b to 2024, with a median of 2012.

5.1.1 Risk of bias

Table 7 provides a summary of the risk of bias assessment for studies in the RRMS population, stratified according to outcome. Results tables in Appendix 4, also include the overall risk of bias for each study for each outcome evaluated.

Domain 1: Risk of bias arising from the randomization process

No studies were judged as being at high risk of bias for the randomisation process, but 14 (35%) were judged at some concerns as they did not report sufficient information on randomisation and/or allocation concealment and there was no evidence of baseline imbalance between intervention groups. All other studies were judged as low risk of bias for this domain. Where studies reported multiple outcomes, risk of bias judgements were the same for all outcomes for this domain.

Domain 2: Risk of bias due to deviations from the intended interventions

Five studies (13%) were judged at high risk of bias due to deviations from the intended intervention – in these studies patients were aware of their treatment assignment and there was a differential rate of treatment discontinuation between the groups, which may have been associated with the outcome. Five studies (13%) were judged as some concerns for this domain as patients were aware of their treatment assignment but there was no evidence of deviations from the intended interventions. Where studies reported multiple outcomes, risk of bias judgements were the same for all outcomes for this domain.

Domain 3: Risk of bias due to missing outcome data

Six studies were judged at high risk of bias due to missing outcome data for the ARR outcome – these studies had a large proportion of missing outcome data (at least 10%) and this was considered to be potentially related to the outcome. Most of these studies did conduct an intention-to-treat (ITT) analysis based either on all randomised patients or on all patients that received at least one dose of the intervention, but studies did not report sufficient details of how the ITT analysis was conducted. One study was judged as some concerns for this domain as although outcome data were missing for 20% of participants, sensitivity analysis suggested that this did not impact results.

Fourteen studies had different risk of bias judgements for the missing outcome domain for other outcomes reported. In eight studies, this was because MRI data were only available for <90% of participants, reasons for this were not reported and this was considered potentially related to the outcome. In six studies the missing outcome data domain was judged as some concerns for risk of bias for ARR, but at low risk of bias for safety data as outcome data were missing for ARR but were available for all, or almost all, participants for the adverse event outcomes.

Domain 4: Risk of bias in measurement of the outcome

Ony two studies were judged at high risk of bias for the measurement of the outcome domain – these specified that outcome assessors were unblinded. Three studies were judged at some concerns as it was unclear whether outcome assessors were blinded. Where studies reported multiple outcomes, risk of bias judgements were the same for all outcomes for this domain.

Domain 5: Risk of bias in selection of the reported result

No studies were judged as being at high risk of bias due to selective outcome reporting, but 14 (35%) were judged at some concerns as no protocol or trial registry entry was available, or the outcome was not specified in the trial registry entry. In the AFFIRM study, only two of the reported outcomes were specified in the trial registry entry – ARR and MRI. The study was therefore judged at low risk of selective outcome reporting for these outcomes but as some concerns for the other outcomes reported – disease progression and quality of life (QoL).

5.1.2 Annualised Relapse Rate (ARR)

All but one (CONFIDENCE[88]) of the 40 studies that reported results for the general RRMS population reported data on ARR and data were available for all interventions evaluated in the general RRMS population. Estimates of ARR for each study arm are summarised in Table 49 (Appendix 3). Studies reported ARR at between 4 and 36 months follow-up, with a median of 24 months follow-up. Included studies defined a "relapse" in different ways. Relapse definitions, broken down into definition components, are summarised in Table 47 (Appendix 3). Relapses were generally defined in terms of:

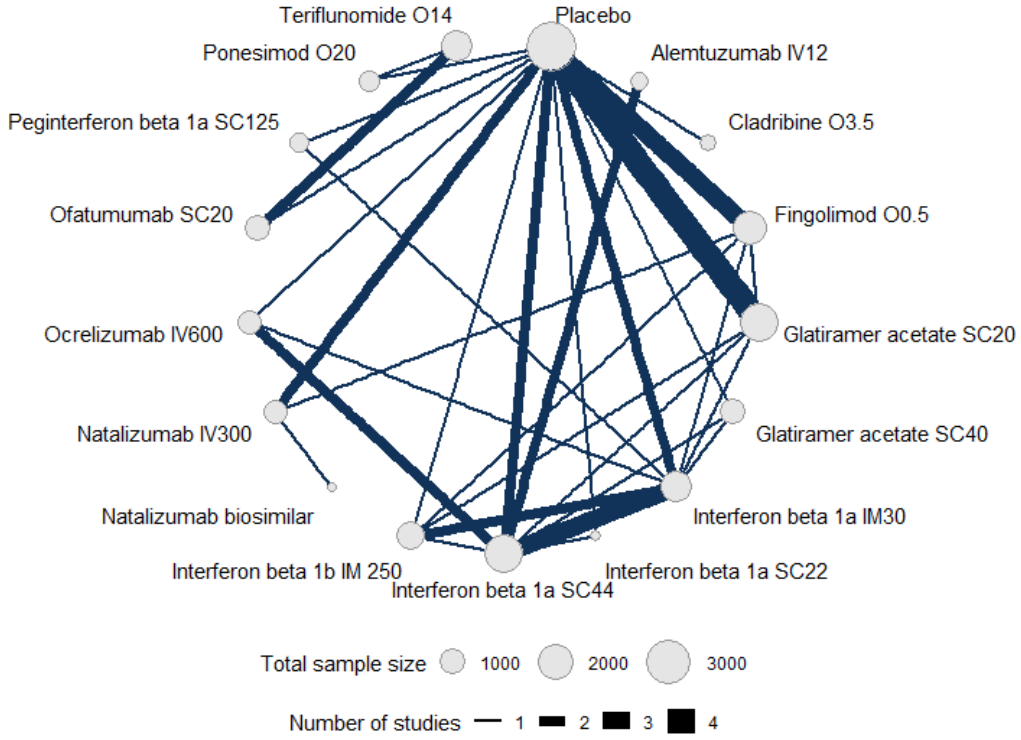
- *Symptoms*: combinations of new, recurrent or worsening of existing symptoms

- *Symptom duration*: at least 24 or 48 hours
- *Exclusion of specific clinical features*: fever, infection, heat intolerance, adverse reaction to medication
- *Neurological examination*: some studies specified that new objective neurologic findings were required, others were more specific specifying an EDSS increase ⩾0.5 points, or increase ⩾1 on two functional scores or ⩾2 on one
- *Previous period of stability* – where required this was always a minimum of 30 days
- *Verification* – some studies specified that verification was required by a specific examiner, and some that this had to be within 7 days of notification of the potential relapse

Our clinical advisors suggested that these definitions were sufficiently similar for it to be appropriate to combine results across studies. For ARR, 17 (44%) studies were at low risk of bias, 15 (38%) had some concerns regarding risk of bias, and 7 (18%) were at high risk of bias.

The 39 studies (20, 810 participants) created a connected network for 17 interventions of interest for this appraisal. The network geometry for this analysis is shown in Figure 3, displaying the treatment nodes and connections, with line thickness representing the number of studies for each comparison and node size the number of patients on each treatment. The placebo group served as the reference group throughout. Natalizumab biosimilar was only directly compared with natalizumab. Natalizumab was also directly compared to placebo and fingolimod and so could be compared to other treatments via these nodes.

Figure 3 Network plot for NMA for ARR



The DIC (77.7 vs 79.9)and residual deviance was also very similar for both fixed and random effects (49.8 vs 49.9 on 55 data points) (Table 59) were both similar for the fixed and random effects models, and indicated good fit for both models with limited heterogeneity in treatment effects across studies. This was confirmed by the heterogeneity standard deviation estimated by the random effects model (tau of 0.05, 95% CrI (0.002, 0.14), Table 59) being very low compared to the average treatment effect on the log rate ratio scale (-0.59 in Table 59). We therefore present results for the fixed effect models for this outcome. Figure 28 (Appendix 5) shows how well each study fits the NMA model. The fixed effects model had a good fit to the data from most studies included in the network, with the exception of the REVEAL and GOLDEN studies, which also had high residual deviance under random effects. REVEAL compared natalizumab with fingolimod and GOLDEN compared fingolimod with interferon beta 1b. Both were multi-centre international studies and there were no clear differences between these two studies and other studies included in the network in terms of study design, outcome definition, or participant characteristics.

Figure 4 shows the Rate ratio (RR) and 95% credible intervals (CrI) for comparison of each intervention included in the network with placebo under the selected fixed effects model, stratified to show estimates from direct and indirect evidence and the overall NMA estimate. Comparison of estimates derived from direct and indirect evidence were similar. Most interventions were associated with a greater reduction (i.e., RR<1 AND 95% CrI excluding 1.00) in the risk of relapses compared to placebo. The exceptions were Teriflunomide and Ponesimod where the risk was similar to placebo. Results were very similar for both random and fixed effects models (Table 59 in Appendix 5). The ranking of

interventions and the probability that each intervention would be ranked first is shown in Table 8, with Table 61 (Appendix 5) showing the probability that each intervention will rank in a specific position. Alemtuzumab had the highest mean ranking (1.4, 95 % CrI 1, 3) and the greatest probability of ranking first (72%) followed by natalizumab (2.2, 95 % CrI 1, 4; 17%). There was greater uncertainty for natalizumab biosimilar which had a 4% probability of ranking first but a mean ranking of 6.6 (95% CrI 1, 15). The different interferon and glatiramer acetate interventions were ranked similarly to each other and as less effective than most of the newer drugs. The exception to this were ponesimod and teriflunomide. Ponesimod had similar efficacy to the interferon and glatiramer acetate interventions, whilst teriflunomide was similar to placebo. Table 60 (Appendix 4) shows the RR (95% CrI) for each intervention pair comparison evaluated in the NMA. This shows that the RR (95% CrI) for natalizumab compared to natalizumab biosimilar, the key comparison for this appraisal, was 0.65 (0.33, 1.23), suggesting no difference between the ARR for these two interventions.

Figure 4 Forest plot of annualised relapse rate (ARR) ratios and 95% credible intervals (fixed effects NMA; RRMS population)

Blue lines indicate result from the NMA, green lines indicate results from direct evidence and purple lines from indirect evidence. P-values relate to comparisons between direct and indirect evidence. Note that the indirect evidence lines are only included if there is also direct evidence.

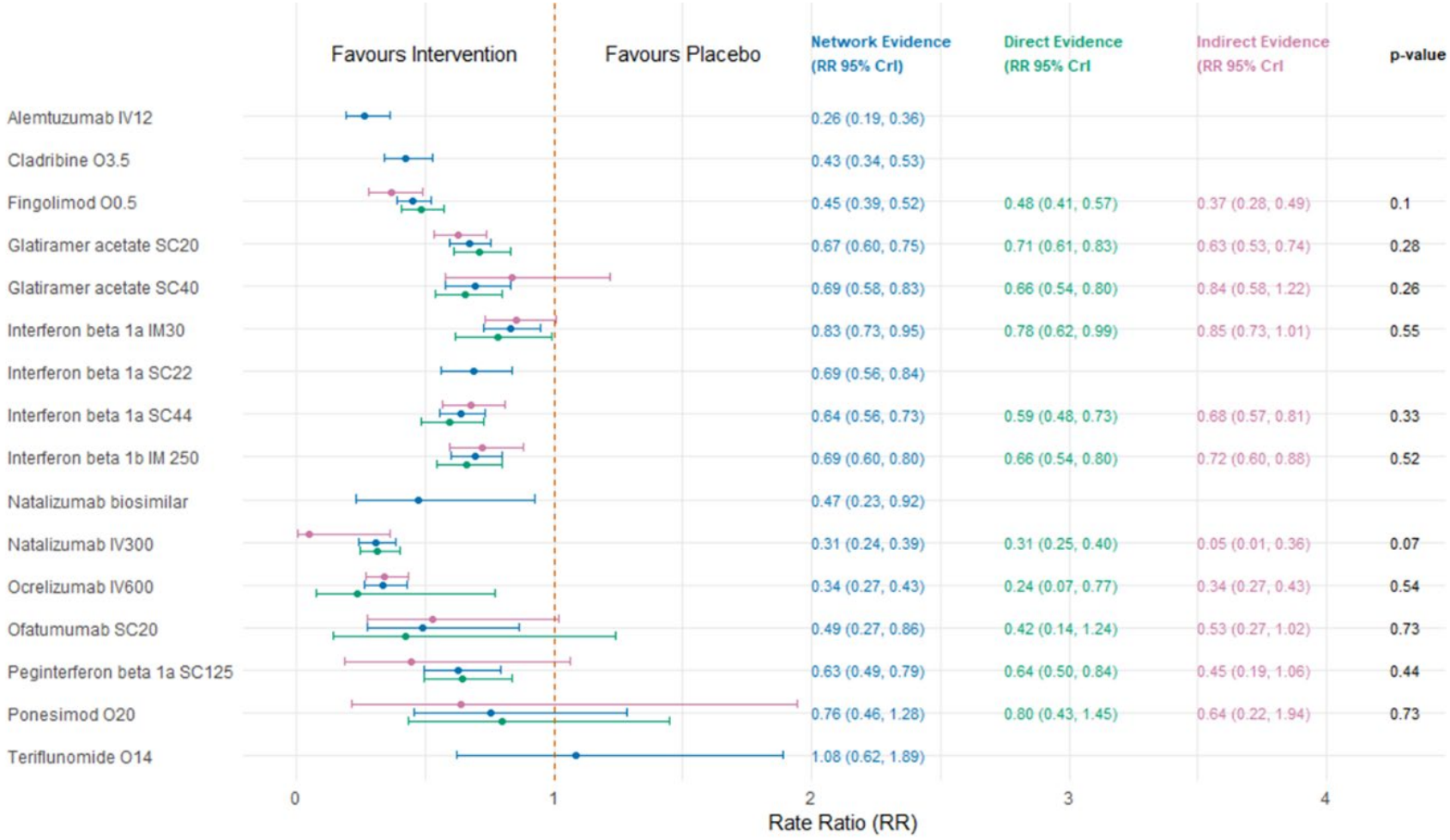


Figure 5 Forest plot of hazard ratios (HR) and 95% credible intervals for time to CDP3 (fixed effects NMA; RRMS population)

Blue lines indicate result from the NMA, green lines indicate results from direct evidence and purple lines from indirect evidence. P-values relate to comparisons between direct and indirect evidence. Note that the indirect evidence lines are only included if there is also direct evidence.

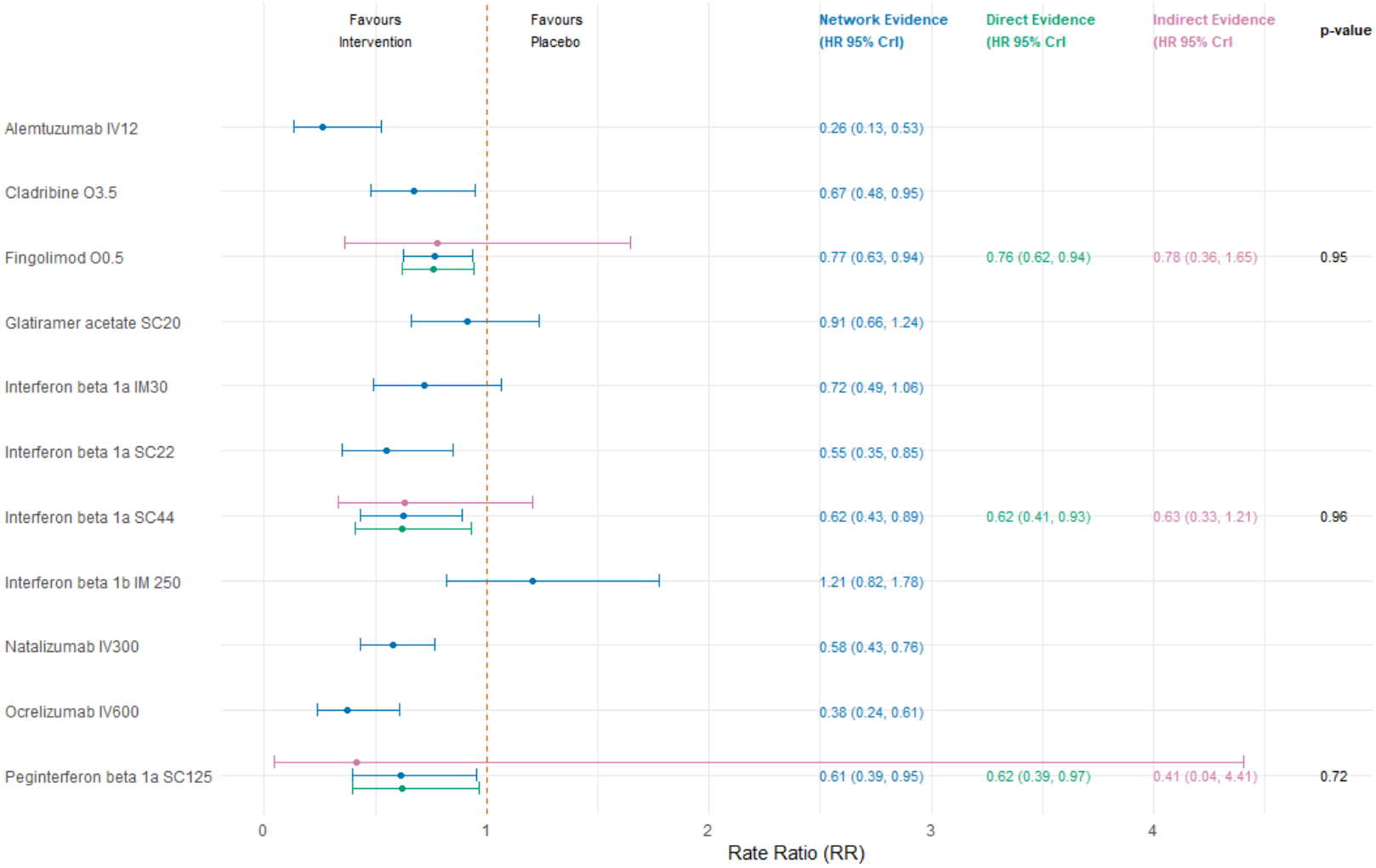


Figure 6 Forest plot of hazard ratios (HR) and 95% credible intervals from fixed effects NMA for time to CDP6 (fixed effects NMA; RRMS population).
Green lines indicate results from direct evidence and purple lines from indirect evidence.

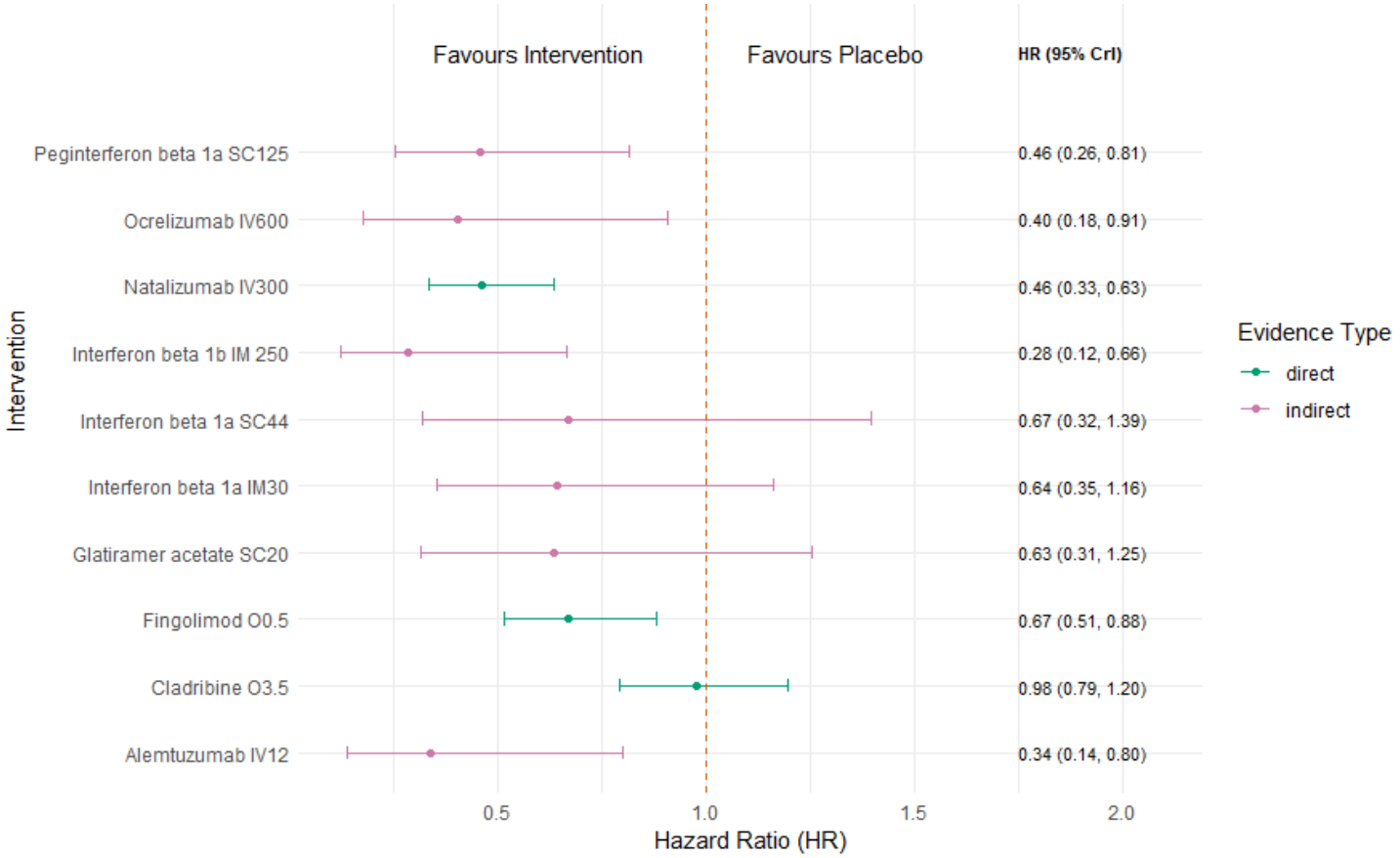


Figure 7 Forest plot of hazard ratios (HR) and 95% credible intervals for time to developing at least one Gd+ MRI lesion (fixed effects NMA; RRMS population)

Blue lines indicate result from the NMA, green lines indicate results from direct evidence and purple lines from indirect evidence. P-values relate to comparisons between direct and indirect evidence. Note that the indirect evidence lines are only included if there is also direct evidence.

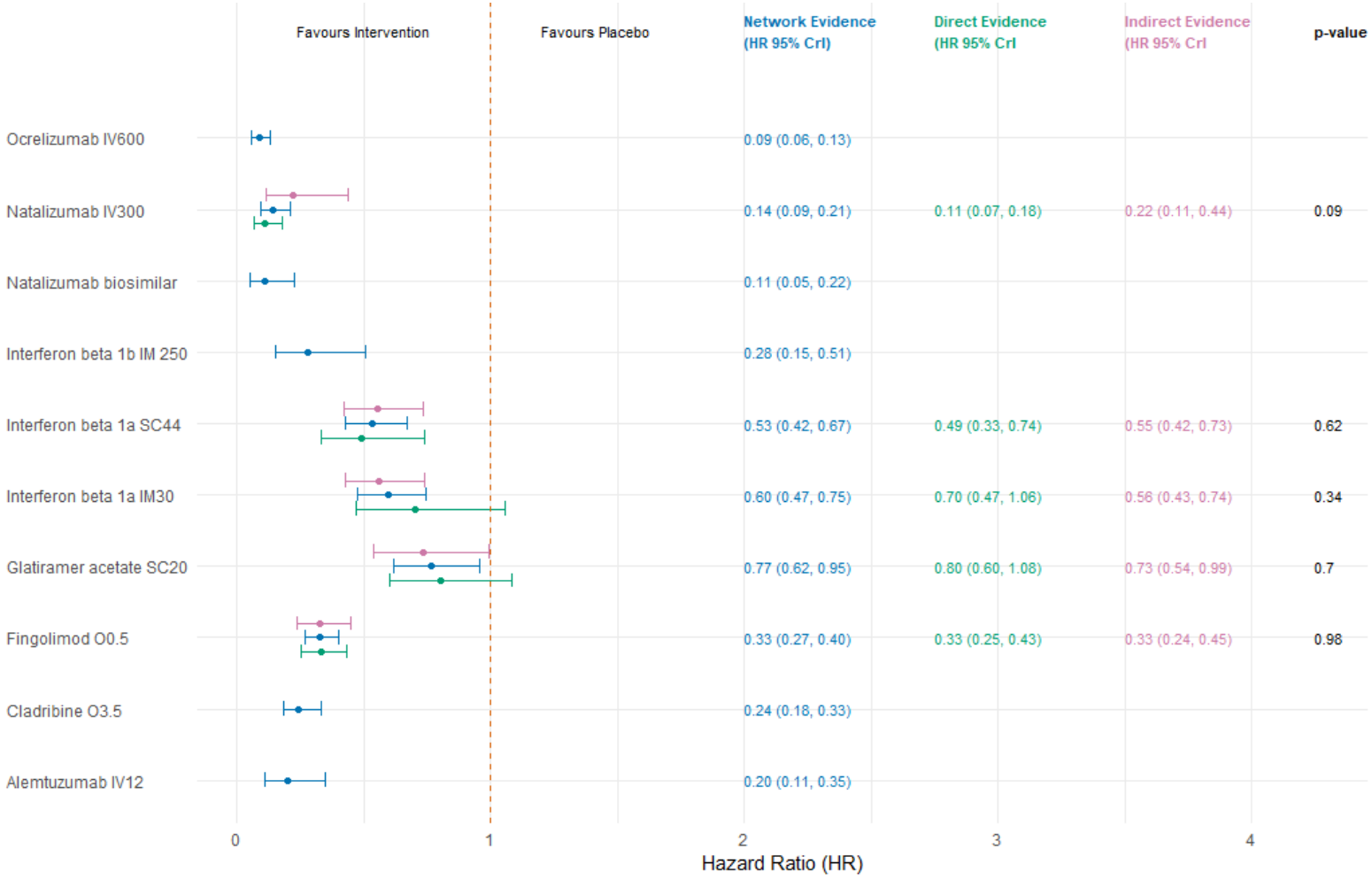


Figure 8 Forest plot of hazard ratios (HR) and 95% credible intervals for time to developing at least one new or enlarging T2 weighted MRI lesions (fixed effects NMA; RRMS population).

Blue lines indicate result from the NMA, green lines indicate results from direct evidence and purple lines from indirect evidence. P-values relate to comparisons between direct and indirect evidence. Note that the indirect evidence lines are only included if there is also direct evidence.

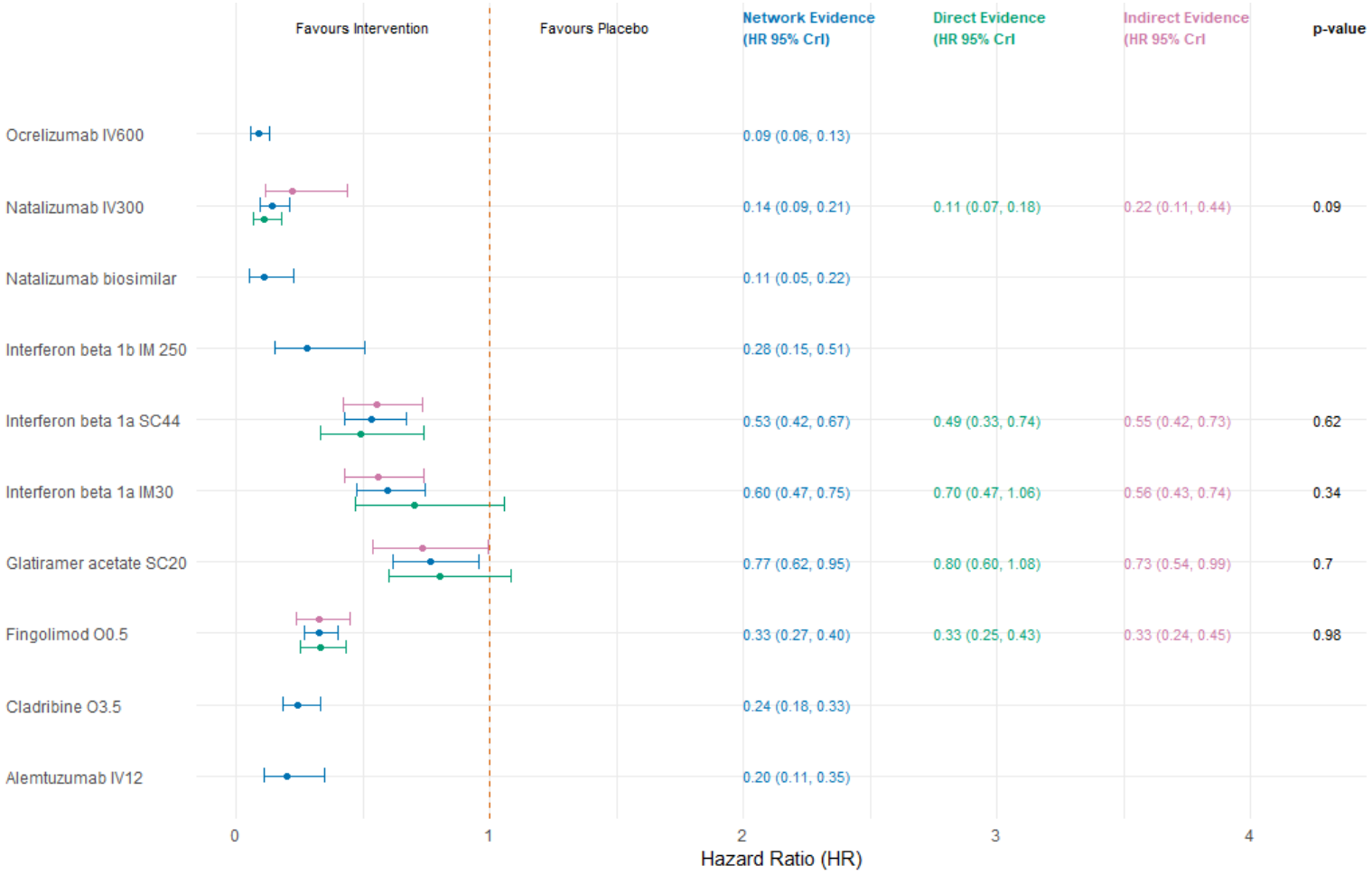


Table 8 Mean ranking of interventions and probability that each intervention would be ranked first from NMAs for each of the outcomes evaluated

Intervention	ARR		CDP3		CDP6		MRI: Gd+		MRI: T2		ARR (highly active)	
	Mean rank (95% CrI)	Pr(best) (%)	Mean rank (95% CrI)	Pr(best) (%)	Mean rank (95% CrI)	Pr(best) (%)	Mean rank (95% CrI)	Pr(best) (%)	Mean rank (95% CrI)	Pr(best) (%)	Mean rank (95% CrI)	Pr(best) (%)
Alemtuzumab IV12	1.4 (1, 3)	72	1.2 (1, 3)	83	2.6 (1, 6)	26	4.2 (2, 7)	68	6.0 (3, 9)	3	3.8 (2, 5)	1
Natalizumab IV300	2.3 (1, 4)	17	4.8 (2, 9)	0	4.3 (1, 8)	5	2.9 (2, 4)	1	3.5 (1, 6)	4	1.8 (1, 5)	53
Natalizumab biosimilar	6.6 (1, 15)	5	NA	NA	NA	NA	2.1 (1, 4)	30	3.0 (1, 7)	31	NA	NA
Ocrelizumab IV600	3.1 (1, 5)	4	2.1 (1, 4)	14	3.6 (1, 7)	5	1.4 (1, 3)	0	2.2 (1, 5)	30	1.8 (1, 5)	44
Ofatumumab SC20	6.6 (2, 14)	2	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Cladribine O3.5	5.0 (3, 7)	0	6.5 (3, 10)	0	10.0 (7, 11)	0	5.1 (4, 7)	0	4.2 (1, 7)	0	4.1 (2, 6)	2
Fingolimod O0.5	5.5 (4, 7)	0	8.1 (5, 10)	0	7.3 (4, 9)	0	6.6 (5, 7)	0	6.4 (5, 8)	0	3.7 (2, 5)	0
Peginterferon beta 1a SC125	9.3 (6, 14)	0	5.5 (2, 10)	1	4.4 (1, 9)	10	NA	NA	8.2 (7, 10)	0	NA	NA
Interferon beta 1a SC44	9.4 (7, 13)	0	5.6 (3, 9)	0	7.6 (4, 11)	0	8.1 (8, 9)	0	NA	NA	6.5 (5, 7)	0
Interferon beta 1a SC22	11.2 (7, 15)	0	4.5 (2, 9)	2	NA	NA	NA	NA	10.6 (8, 12)	0		
Interferon beta 1a IM30	14.6 (13,16)	0	7.4 (3, 11)	0	7.2 (4, 10)	0	8.9 (8, 9)	0	9.2 (7, 11)	0		
Glatiramer acetate SC20	10.7 (8, 14)	0	9.6 (6, 11)	0	7.0 (4, 11)	0	10.0 (10, 10)	0	NA	NA	NA	NA
Glatiramer acetate SC40	11.3 (7, 15)	0	NA	NA	NA	NA	NA	NA	9.8 (8, 11)	0	NA	NA
Interferon beta 1b IM 250	11.4 (8, 15)	0	11.7 (10, 12)	0	1.9 (1, 5)	54	5.7 (3, 7)	0	3.1 (1, 8)	32	NA	NA
Ponesimod O20	12.3 (6, 16)	0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Teriflunomide O14	16.1 (10, 17)	0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Placebo	16.2 (15, 17)	0	10.8 (10, 12)	0	10.2 (7, 11)	0	11.0 (11, 11)	0	11.8 (11, 12)	0	6.4 (6, 7)	0

Sensitivity analysis for ARR

We had intended to conduct a meta-regression to investigate potential reasons for heterogeneity. However, as heterogeneity was low and covariates were broadly similar across groups this was not appropriate. Instead, we conducted a sensitivity analysis restricted to studies judged at low risk of bias. This analysis included 17 studies and created a connected network (Figure 29, Appendix 5), although data were not available for the following interventions: alemtuzumab, cladribine, interferon beta 1a (SC22), or interferon beta 1b. Estimates of RR for the interventions for which data were available were very similar to those obtained for the full set of studies, suggesting that risk of bias in these studies did not have a substantial impact on results. We investigated whether it was possible to carry out analyses separately for studies that reported data for 6, 12 and 24 month follow-up, but there were insufficient data and networks did not connect for follow-up of less than 24 months; the network for 24 months was almost the same as that for all studies combined.

5.1.3 Disease Progression

Only 23 of the 40 studies that reported results for the general RRMS population reported data on disease progression – 12 studies reported both CDP3 and CDP6, six studies reported CDP3 only and five reported CDP6 only. Estimates of CDP for each study arm are summarised in Table 49 (Appendix 4). Studies reported disease progression at between 6 and 24 months follow-up, with a median of 24 months follow-up. Included studies defined disease progression in different ways. Disease progression definitions, broken down into definition components, are also summarised in Table 49 (Appendix 4). All studies defined criteria for disease progression based on increase in EDSS scores and baseline EDSS scores – some simply specified an increase of at least one point regardless of baseline EDSS, others specified an increase of at least 1.5 points in those with a baseline EDSS score of 0 with an increase of at least one point in those with an EDSS score of at least one, and some specified an increase in EDSS score of 0.5 points in those with higher baseline EDSS scores (most commonly a baseline EDSS of more than 5 but in some this was more than 4.5 or 5.5). Our clinical advisors suggested that these definitions were sufficiently similar for it to be appropriate to combine results across studies.

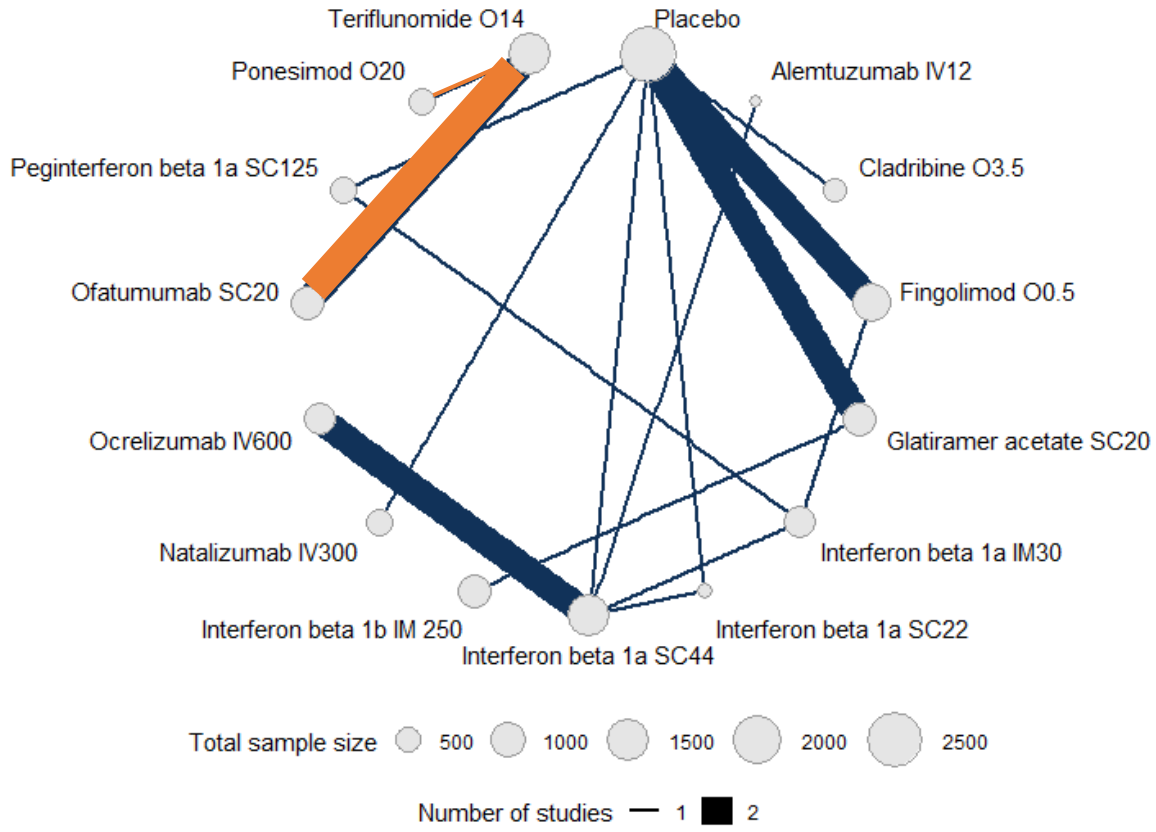
Studies reporting data on CDP3 and CDP6 did not create a completely connected network for either outcome – for both outcomes, teriflunomide, ponesimod and ofatumumab did not connect to the network. We were therefore unable to include these interventions in the NMA. Studies of natalizumab biosimilar and glatiramer acetate SC40 did not report on disease progression and so these interventions were also excluded from the networks for CDP3 and CDP6.

Of the 20 studies that were included in the NMAs for CDP3 and CDP6, six studies were judged at low risk of bias, nine at some concerns regarding risk of bias and five at high risk of bias.

CDP3

Following exclusion of the three studies that did not connect to the network (OPTIMUM, ASCLEPIOS I and ASCLEPIOS II), the remaining 15 studies (10, 635 participants) created a connected network for 11 interventions. The network geometry for this analysis is shown in Figure 9, displaying the treatment nodes and connections, with line thickness representing the number of studies for each comparison and node size the number of patients on each treatment. The placebo group served as the reference group throughout.

Figure 9 Network plot of CDP3 NMA including disconnected treatments (shown with orange lines)



The DIC for the fixed effects model was slightly lower than for the random effects model (22.8 vs 25.1), suggesting that this model gives a better trade off between fit and complexity for the dataset (Table 64 in Appendix 3). The residual deviance was also lower for the fixed effects model than for the random effects model (11.8 vs 12.8 on 16 data points) indicating better fit for the fixed effects model. The DIC and residual deviance together indicate limited heterogeneity in treatment effects across studies. This was confirmed by the heterogeneity standard deviation estimated by the random effects model (tau (95% CrI) of 0.14 (0.005, 0.50), Table 64) being low compared to the average treatment effect on the log rate ratio scale (-0.48). We therefore present results for the fixed effect models for this outcome.

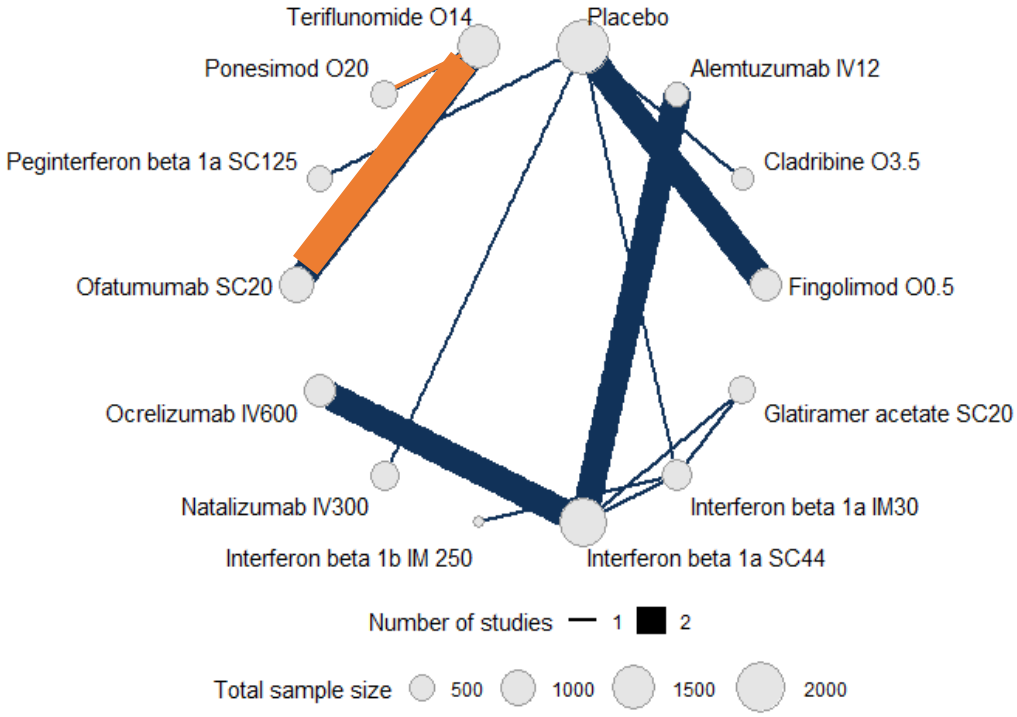
Figure 30 (Appendix 5) shows how well each study fits the NMA model. Both random and fixed effects model had a good fit to the data from all studies included in the network.

Figure 5 shows the HR and 95% credible intervals (CrI) for comparison of each intervention included in the network with placebo under the selected random effects model, stratified to show estimates from direct and indirect evidence and the overall NMA estimate. Comparison of estimates derived from direct and indirect evidence were similar. Alemtuzumab, ocrelizumab, natalizumab, fingolimod, cladribine and interferon beta 1a (SC22 and SC44) were associated with a greater reduction (i.e., HR<1 AND 95% CrI excluding 1.00) in the risk of CDP3 compared to placebo. There was little evidence to suggest a difference in the risk of CDP3 between those treated with glatiramer acetate or other interferon beta interventions and placebo. Results were very similar for both random and fixed effects models (Table 64 in Appendix 5). The ranking of interventions and the probability that each intervention would be ranked first is shown in Table 8 with Table 61 (Appendix 5) showing the probability that each intervention will rank in a specific position. Alemtuzumab had the highest mean ranking (1.2, 95 % CrI 1, 3) and the greatest probability of ranking first (83%) followed by ocrelizumab (2.1, 95 % CrI 1, 4; 14%). All other interventions in the network, including natalizumab, had a <5% probability of ranking first. Table 65 (Appendix 4) shows the HR (95% CrI) for each intervention pair comparison evaluated in the NMA.

CDP6

In addition to studies of natalizumab biosimilar and glatiramer acetate SC40 not reporting any data on disease progression, the studies of interferon beta 1a SC22 did not report on CDP6 and so this intervention was also excluded from the CDP6 network. The remaining 14 studies (n=9,306) created a connected network for the remaining 10 interventions of interest for this appraisal. The network geometry for this analysis is shown in Figure 10, displaying the treatment nodes and connections, with line thickness representing the number of studies for each comparison and node size the number of patients on each treatment. The placebo group served as the reference group throughout.

Figure 10 Network plot of CDP6 NMA including disconnected treatments (shown with orange lines)



The DIC for the random and fixed effects models were very similar (27.9 vs 28.0) (Table 67). The residual deviance was close to the number of data points for both studies (14.9 vs 17.9 on 14 data points) indicating a good fit for both models. The DIC and residual deviance together indicate limited heterogeneity in treatment effects across studies. The heterogeneity standard deviation estimated by the random effects model (tau (95% CrI) of 0.39 (0.02, 1.19) in Table 64) suggested moderate heterogeneity. Figure 31 (Appendix 5) shows how well each study fits the NMA model. The fixed effects model had a good fit to the data from all studies included in the network. We therefore present results for the fixed effect model for this outcome.

Figure 6 shows the HR and 95% credible intervals (CrI) for comparison of each intervention included in the network with placebo under the selected random effects model. Note that for this analysis there were no interventions for which both direct and indirect evidence were available – the plot shows which estimates were derived from each type of evidence. alemtuzumab, fingolimod, interferon beta 1b, natalizumab, ocrelizumab, peginterferon beta 1a SC125 were associated with a lower risk of CDP6 than placebo. Results were similar for both random and fixed effects models (Table 67 in Appendix 5), although credible intervals were wider for the random effects model. There was considerable uncertainty in the ranking of interventions and the probability that each intervention would be ranked first (Table 8 and Table 72 (Appendix 5)). Table 71 (Appendix 4) shows the HR (95% CrI) for each intervention pair comparison evaluated in the NMA.

CDP3/6 combined

We conducted a sensitivity analysis where we included the six studies that only reported CDP3 in the analysis for CDP6 to maximise the number of studies that contributed to this analysis. We included 20 studies (n=13,298) evaluating 11 interventions in this analysis. The network geometry for this analysis is the same as for the CDP3 analysis as this combined analysis allowed us to include interferon beta 1a SC22 which was not included in the CDP6 analysis (Figure 9). Results were very similar to those obtained for CDP6 alone (Appendix 5), although with narrower credible intervals.

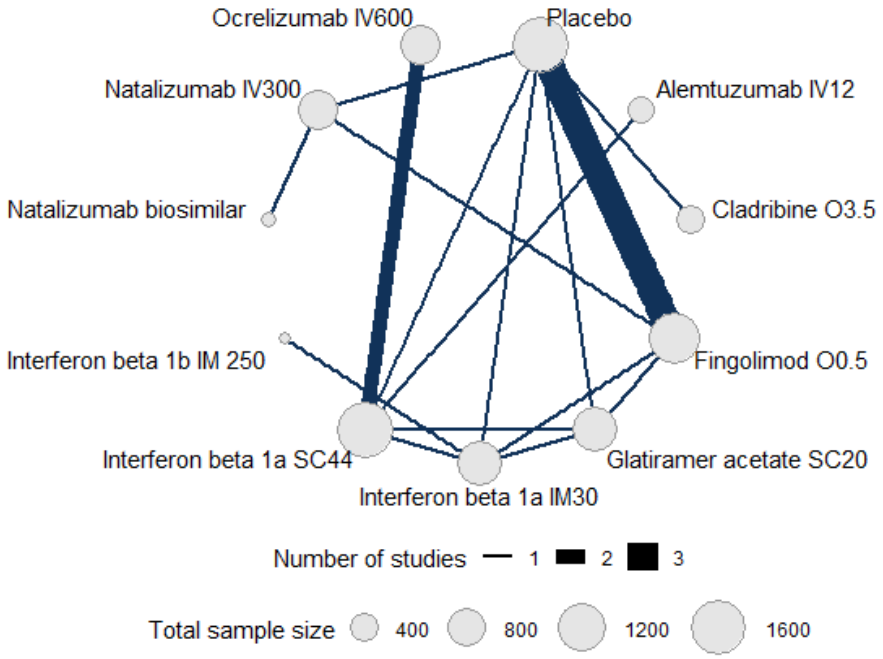
5.1.4 MRI Outcomes

Twenty studies reported data on at least one of the two MRI outcomes of interest for this appraisal: the proportion of patients with gadolinium enhancing (Gd+) or new or enlarging T2 lesions. All but one of these (PRISMS) reported data on Gd+ lesions, and all but three (CombiRx, GATE and Multiple Sclerosis Collaborative Research Group) reported data on T2 lesions. For Gd+ lesions, most studies reported on the proportion of patients with "any" Gd+ lesions, some reported only on new lesions. Studies reported MRI outcomes at between 4 and 24 months follow-up, with a median of 24 months. There were no data on MRI outcomes of interest for studies of the following interventions and so these were not able to be included in the NMAs for these outcomes: ofatumumab, glatiramer acetate (SC40), ponesimod, teriflunomide, and peginterferon beta 1a. Data were only available for T2 lesions for interferon beta 1a (SC22) and so this was only included for this outcome. Natalizumab biosimilar was only directly compared with natalizumab. Natalizumab was also directly compared to placebo and fingolimod and so could be compared to other treatments via these nodes.

Gadolinium (Gd+) enhancing lesions

Nineteen studies (9, 471 participants) reported data on Gd+ lesions and created a connected network for 11 interventions of interest for this appraisal (Figure 11). The placebo group served as the reference group throughout.

Figure 11 Network plot for NMA for proportion of participants with Gd+ lesions



The DIC (27.9 vs 28.5) and residual deviance (17.8 vs 16.5 on 19 data points) were similar for both fixed and random effects models and indicated good fit for both models with limited heterogeneity (Table 73). This was confirmed by the heterogeneity standard deviation estimated by the random effects model (tau (95% CrI) of 0.11 (0.006, 0.32) in Table 73). We therefore present results for the fixed effect models for this outcome. Figure 28 (Appendix 5) shows how well each study fits the NMA model. The fixed effects model had a good fit to the data from all studies included in the network.

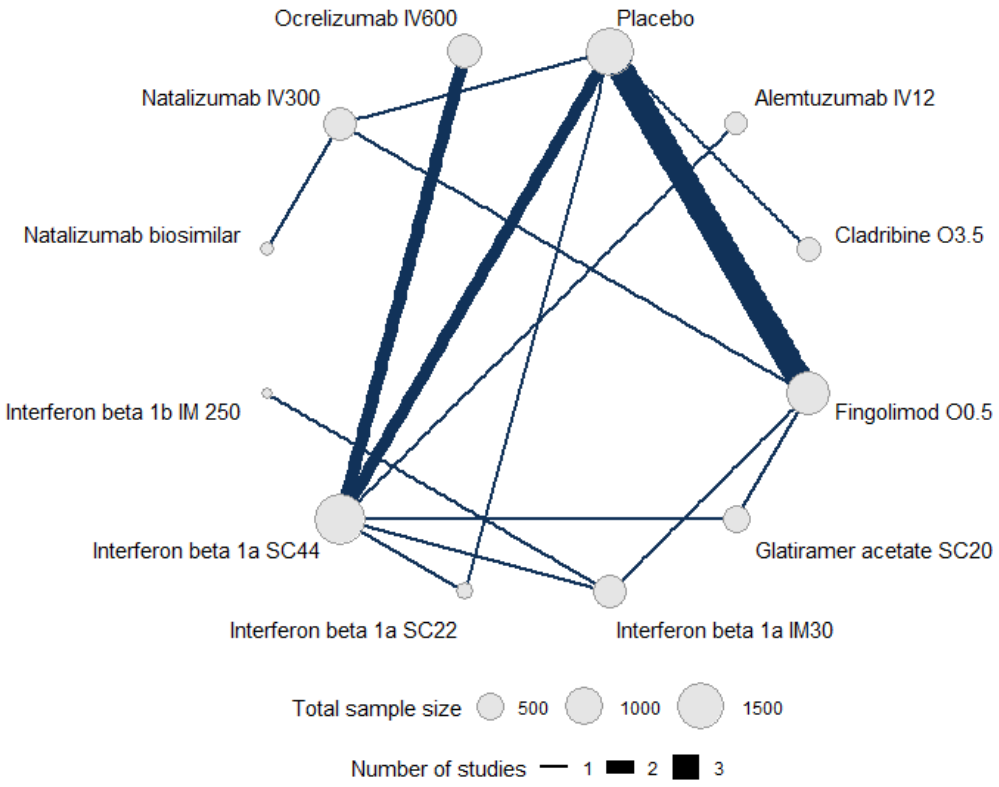
Figure 7 shows the hazard ratio (HR) and 95% credible intervals (CrI) for comparison of each intervention included in the network with placebo under the selected fixed effects model, stratified to show estimates from direct and indirect evidence and the overall NMA estimate. Comparison of estimates derived from direct and indirect evidence were similar. All interventions were associated with a greater reduction (i.e., HR<1 AND 95% CrI excluding 1.00) in the risk of developing Gd+ lesions compared to placebo. Results were very similar for both random and fixed effects models (Table 73 in Appendix 5). The ranking of interventions and the probability that each intervention would be ranked first is shown in Table 8, with Table 75 (Appendix 5) showing the probability that each intervention will rank in a specific position. Ocrelizumab had the highest mean ranking (1.4, 95 % CrI 1, 3) and the greatest probability of ranking first (68%) followed by natalizumab biosimilar (2.1, 95 % CrI 1, 4; 30%) and natalizumab (2.9, 95% CrI 2, 4; 1%). All other interventions had a 0% probability of ranking first. The different interferon and glatiramer acetate interventions were ranked similarly to each other and as less effective than the newer drugs. Table 74 (Appendix 4) shows the HR (95% CrI) for each intervention pair comparison evaluated in the

NMA. This shows that the HR (95% CrI) for natalizumab compared to natalizumab biosimilar, the key comparison for this appraisal, was 1.29 (0.69, 2.37), suggesting no difference between the HR for these two interventions.

New or enlarging T2 weighted lesions

The 17 studies (8,883 participants) that reported data on T2 weighted lesions created a connected network for 12 interventions of interest for this appraisal (Figure 1). The placebo group served as the reference group throughout.

Figure 12 Network plot for NMA for proportion of participants with new or enlarging T2 lesions



The DIC (26.4 vs 27.9) and residual deviance (14.5 vs 15.6 on 18 data points) were very similar for both fixed and random effects models and indicated good fit for both models with limited heterogeneity in treatment effects across studies (Table 76). This was confirmed by the heterogeneity standard deviation estimated by the random effects model (tau 95% of 0.07 (0.002, 0.25) in Table 76). We therefore present results for the fixed effect models for this outcome. Figure 34 (Appendix 5) shows how well each study fits the NMA model. The fixed effects model had a good fit to the data from all studies included in the network, except the IMPROVE study. This study reported data at very short follow-up (4 months) and compared interferon beta 1a SC44 to placebo.

Figure 7 shows the hazard ratio (HR) and 95% credible intervals (CrI) for comparison of each intervention included in the network with placebo under the selected fixed effects model, stratified to show estimates from direct and indirect evidence and the overall NMA estimate. Comparison of estimates derived from direct and indirect evidence were similar. All interventions except interferon beta 1a SC44 were associated with a greater reduction (i.e., HR<1 AND 95% CrI excluding 1.00) in the risk of relapses compared to placebo. Results were very similar for both random and fixed effects models (Table 76 in Appendix 5). The ranking of interventions and the probability that each intervention would be ranked first is shown in Table 8, with Table 81 (Appendix 5) showing the probability that each intervention will rank in a specific position. Ocrelizumab had the highest mean ranking (2.2, 95 % CrI 1, 5) and a similar probability of ranking first (30%) to natalizumab biosimilar (3.0, 95 % CrI 1, 7; 31%) and interferon beta 1b (3.1, 95% CrI 1, 8; 32%). Natalizumab had the next highest ranking (3.5, 95% CrI 1, 6) and a 4% probability of ranking first. All other interventions had a 0% probability of ranking first. The different interferon beta 1a and glatiramer acetate interventions were ranked similarly to each other and as less effective than the newer drugs. Table 77 (Appendix 4) shows the HR (95% CrI) for each intervention pair comparison evaluated in the NMA. This shows that the HR (95% CrI) for natalizumab compared to natalizumab biosimilar, the key comparison for this appraisal, was 1.07 (0.73, 1.57) suggesting no difference between the HR for these two interventions.

5.1.5 Adverse events

All but four of the included studies reported at least one of the adverse events outcomes of interest. Etemedifir 2006 and Calabrese 2012 did not report any data on adverse events; INCOMIN and PRISMS only reported data on the incidence of specific adverse events and so could not be included in our synthesis. Adverse events reported in the studies included a range of symptoms and reactions. These encompass injection site issues such as erythema, pain, pruritus, swelling, bruising, and immediate post-injection reactions, as well as systemic symptoms like influenza-like illness, chills, pyrexia, and fatigue. Common neurological and musculoskeletal complaints included headache, migraine, myalgia, arthralgia, dizziness, blurred vision, paraesthesia, and muscular weakness. Infections were frequently noted, including nasopharyngitis, urinary tract infections, upper respiratory tract infections, oral herpes, bronchitis, sinusitis, and meningitis. Other adverse events span gastrointestinal symptoms like nausea, diarrhoea, constipation, and abdominal pain, alongside more serious conditions such as hepatic toxicity, liver failure, and neoplasms. Psychiatric conditions, particularly depression and anxiety, were reported, as were dermatological issues like rash, alopecia, and hypoesthesia. Cardiovascular effects such as hypertension and bradycardia were also mentioned. Additionally, rare but serious conditions included autoimmune events and thyroid disorders.

Mortality (from any cause) was only reported in 27 trials, and where reported this was very rare. The majority of studies reported no deaths, with a maximum of 2 deaths in any treatment group. Only four studies reported on progressive multifocal leukoencephalopathy

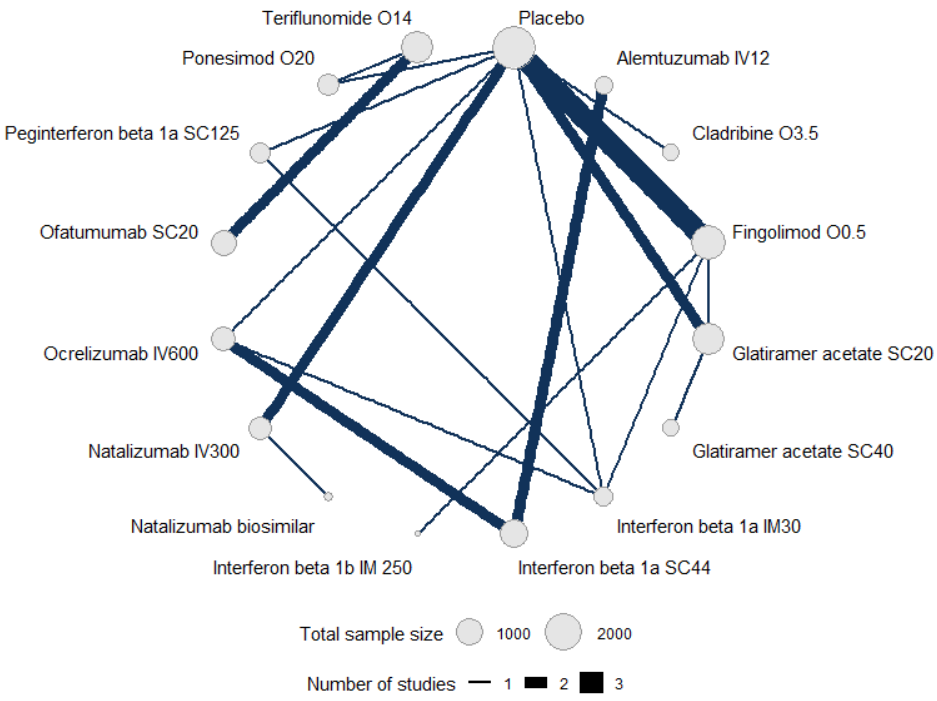
(PML) – none of these reported any cases of PML. None of the included studies reported data on grade 3-4 AEs.

Twenty studies were judged at low risk of bias for adverse events, eleven were judged at some concerns and five were judged at high risk of bias.

Any AEs

Twenty four studies (9, 471 participants) reported data on the incidence of any adverse events. These studies created a connected network for 16 interventions of interest for this appraisal (Figure 13) – the only intervention for which data on any AEs were not available was interferon beta 1a (SC22). The placebo group served as the reference group throughout. Follow-up duration ranged from 6 to 24 months with a median of 18 months – slightly shorter than for the effectiveness outcomes.

Figure 13 Network plot for NMA for any AEs



The DIC for the fixed effects model was lower than for the random effects model (32.6 vs 34.8), suggesting that this model gives a better trade off between fit and complexity for the dataset (Table 79). The residual deviance was also lower for the fixed effects model (17.8 vs 18.7 on 25 data points). However both indicated good fit for their respective models. The DIC and residual deviance together indicate limited heterogeneity in treatment effects across studies. This was confirmed by the heterogeneity standard deviation estimated by the random effects model (tau (95% CrI) of 0.03 (0.002, 0.11) in Table 79). We therefore present results for the fixed effects model for this outcome. Figure 35 (Appendix 5) shows

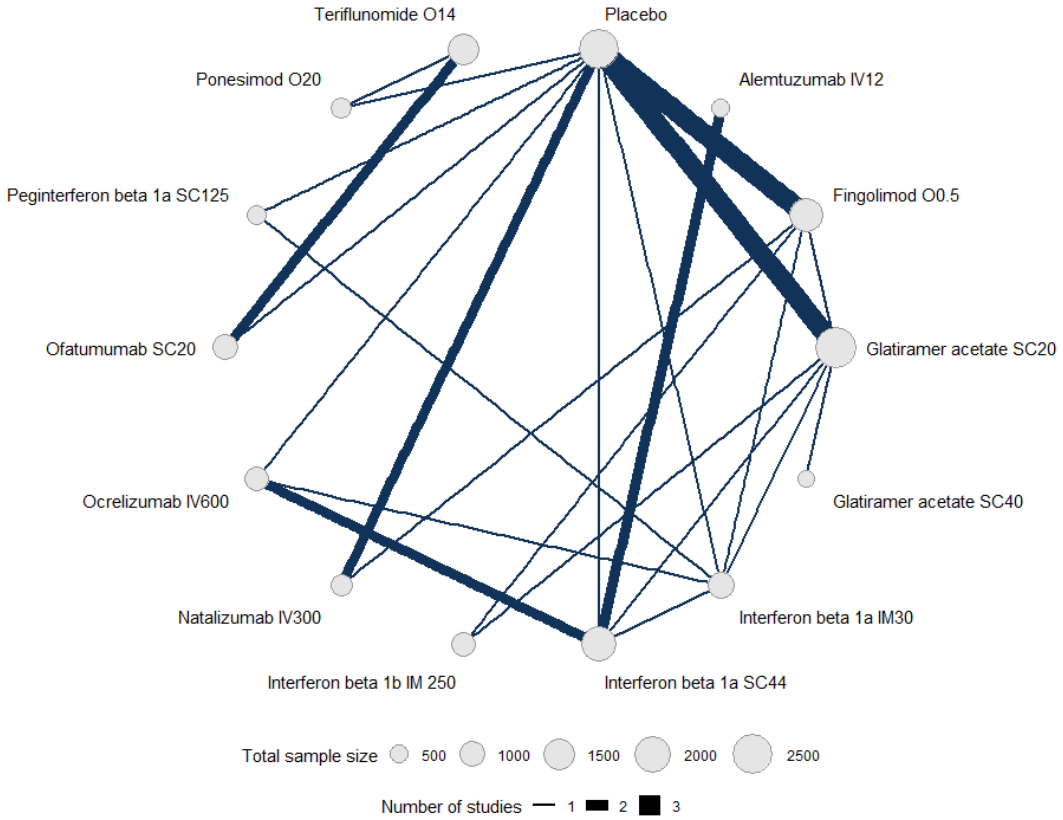
how well each study fits the NMA model. The fixed effects model had a good fit to the data from all studies included in the network.

Figure 16 shows the hazard ratio (HR) and 95% credible intervals (CrI) for comparison of each intervention included in the network with placebo under the selected fixed effects model, stratified to show estimates from direct and indirect evidence and the overall NMA estimate. Comparison of estimates derived from direct and indirect evidence were similar. There was no evidence of a difference in the risk of developing any AE between any of the interventions and placebo (i.e., HR<1 AND 95% CrI excluding 1.00). Results were very similar for both random and fixed effects models (Table 79 in Appendix 5). Table 81 (Appendix 5) showing the probability that each intervention will rank in a specific position with better rankings suggesting a lower risk of AEs. Table 80 (Appendix 4) shows the HR (95% CrI) for each intervention pair comparison evaluated in the NMA. This shows that the HR (95% CrI) for natalizumab compared to natalizumab biosimilar, the key comparison for this appraisal, was 1.06 (0.77, 1.46) suggesting no difference between the HR for these two interventions.

Serious AEs

Thirty studies (18, 748 participants) reported data on the incidence of serious adverse events (SAEs). These studies created a connected network for 14 interventions of interest for this appraisal (Figure 13) – data on any SAEs were not available for interferon beta 1a (SC22), cladribine or natalizumab biosimilar. The placebo group served as the reference group throughout. Duration of follow-up ranged from 6 to 36 months with a median of 18 months.

Figure 14 Network plot for NMA for serious AEs



The DIC for the fixed effects model was slightly lower than for the random effects model (36.8 vs 37.8), suggesting that this model gives a better trade off between fit and complexity for the dataset (Table 82). Both models have residual deviances lower than the number of data points (23.7 vs 23.1 on 31 data points) with the fixed effects model suggesting a slightly better fit. The DIC and residual deviance together indicate limited heterogeneity in treatment effects across studies. This was confirmed by the heterogeneity standard deviation estimated by the random effects model (tau (95% CrI) of 0.11 (0.004, 0.32) in Table 82). We therefore present results for the fixed effect models for this outcome. Figure 36 shows how well each study fits the NMA model. Although FREEDOMS shows a higher residual deviance than the rest of studies, it's 95% CrI fall within the acceptable range, so we consider the fixed effects model had a good fit to the data from all studies included in the network.

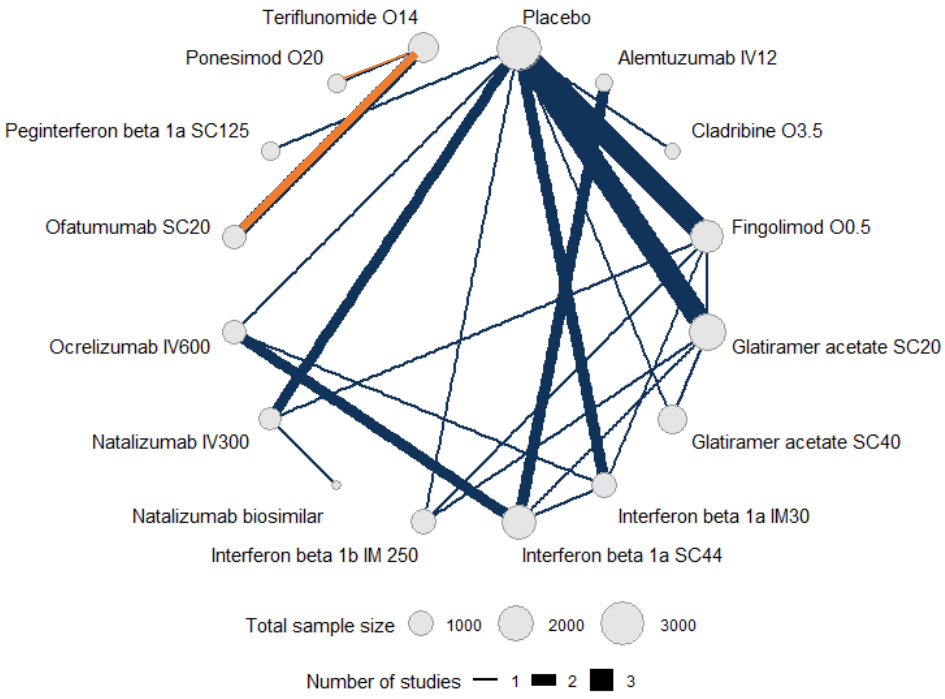
Figure 17 shows the hazard ratio (HR) and 95% credible intervals (CrI) for comparison of each intervention included in the network with placebo under the selected fixed effects model, stratified to show estimates from direct and indirect evidence and the overall NMA estimate. Comparison of estimates derived from direct and indirect evidence were similar. There was no evidence of a difference in the risk of developing serious AE between any of the interventions and placebo (i.e., HR<1 AND 95% CrI excluding 1.00). Results were very similar for both random and fixed effects models (Table 82 Comparison of results from fixed

and random effects NMA for SAEs (RRMS population)Table 79 in Appendix 5). Table 84 (Appendix 5) shows the probability that each intervention will rank in a specific position. Table 83 shows the HR (95% CrI) for each intervention pair comparison evaluated in the NMA. There was no data on frequency of serious AE for natalizumab biosimilar, so a comparison to Natalizumab was not possible.

AEs leading to treatment discontinuation

Twenty nine studies (17,892 participants) reported data on the incidence of AEs leading to treatment discontinuation. These did not create a completely connected network – teriflunomide, ponesimod and ofatumumab did not connect to the network (Figure 15). We were therefore unable to include these interventions in the NMA. Data on any AEs leading to treatment discontinuation were not available for interferon beta 1a (SC22) and this was also not included in the network. The placebo group served as the reference group throughout.

Figure 15 Network plot for NMA for AEs leading to treatment discontinuation including disconnected treatments (shown with orange lines)



The DIC for the fixed effects model was slightly lower than for the random effects model (41.2 vs. 41.7), suggesting that this model gives a slightly better trade-off between fit and complexity for the dataset (Table 85). Both models have residual deviances close to the number of data points (29.2 vs 26 on 28 data points) with the fixed effects model suggesting a slightly better fit. The DIC and residual deviance together indicate limited heterogeneity in treatment effects across studies. This was confirmed by the heterogeneity standard

deviation estimated by the random effects model (tau (95% CrI) of 0.27 (0.01, 0.69) in Table 85). We therefore present results for the fixed effect models for this outcome. Figure 37 Model fit for discontinuation due to AEs assessed by individual study residual deviance (fixed effects analysis; RRMS population) shows how well each study fits the NMA model. Although FREEDOMS and TRANSFORMS show a higher residual deviance than the rest of studies, its 95% CrI fall within the acceptable range. GATE shows a high residual deviance, but this is a very small study, so we consider the fixed effects model had a good fit to the data from studies included in the network in general.

Figure 18 shows the hazard ratio (HR) and 95% credible intervals (CrI) for comparison of each intervention included in the network with placebo under the selected fixed effects model, stratified to show estimates from direct and indirect evidence and the overall NMA estimate. Comparison of estimates derived from direct and indirect evidence were similar. There was evidence of an increased risk of presenting with an adverse event leading to discontinuation for fingolimod HR (95% CRI), glatiramer acetate, interferon beta 1a SC44, interferon beta 1b, and peginterferon beta 1a compared with placebo. There was no evidence of a difference in the risk of AEs leading to treatment discontinuation between any of the other interventions and placebo. Results were very similar for both random and fixed effects models (Table 82in Appendix 5). Table 87 (Appendix 5) shows the probability that each intervention will rank in a specific position. Table 86 shows the HR (95% CrI) for each intervention pair comparison evaluated in the NMA. This shows that the HR (95% CrI) for natalizumab compared to natalizumab biosimilar, the key comparison for this appraisal, was 0.48 (0.13, 1.76) suggesting no difference between the HR for these two interventions.

Treatment related AEs

Only eight studies (3,361 participants) reported data on treatment related adverse events. These did not create a connected network and so an NMA was not possible. Instead, we provide a summary of the results from these studies in Table 9. Interventions evaluated included Peginterferon beta 1a, natalizumab, natalizumab biosimilar, ofatumumab, ocrelizumab, glatiramer acetate, interferon beta 1a, and peginterferon beta 1a. There was no difference between interventions in the proportion of treatment related AEs for any of the studies.

Table 9 Summary of studies that reported data on treatment related AEs, including RR and 95% CIs for the difference in risk between intervention and comparator groups

Study Name	Intervention	Comparator	Follow-up	RR (95% CI)
ADVANCE[80]	Peginterferon beta 1a SC125	Placebo	12	1.69 (0.54, 0.65)
ANTELOPE[76]	Natalizumab IV300	Natalizumab biosimilar	6	1.11 (0.56, 1.46)
APOLITOS[69]	Ofatumumab SC20	Placebo	6	0.86 (0.87, 1.54)
CONFIDENCE[88]	Glatiramer acetate SC40	Glatiramer acetate SC20	6	1.0 (0.83, 1.21)
Kappos 2011[100]	Interferon beta 1a IM30	Placebo	6	0.76 (0.83, 2.09)
	Ocrelizumab IV600	Placebo	6	0.67 (0.92, 2.44)
PEGINTEGRITY[65]	Peginterferon beta 1a SC125	Interferon beta 1a IM30	24	0.94 (0.9, 1.25)
REGARD[103]	Glatiramer acetate SC20	Interferon beta 1a SC44	24	0.99 (0.89, 1.11)

Study Name	Intervention	Comparator	Follow-up	RR (95% CI)
REVEAL[78]	Natalizumab IV300	Fingolimod O0.5	6	0.72 (0.95, 2.04)

5.1.6 Quality of life

Only eight studies provided data on quality of life assessed using the EQ-5D or SF-36 tools. Results from these studies are summarised in Table 57 (Appendix 4). Six studies provided data on the SF-36 (ADVANCE, CARE-MS I, CONFIRM, AFFIRM, OPERA I, OPERA II) and five studies provided data on EQ-5D (CLARITY, FREEDOMS II, ADVANCE, CARE-MS I, CONFIRM). Four studies were judged at high risk of bias, three were at low risk of bias, and one was at low concerns for the EQ-5D visual analogue scale and some concerns for the EQ-5D utility score and SF-36 measures.

There was no evidence of a difference between groups for any of the studies that reported data on the EQ-5D mean utility or VAS scores. Interventions evaluated in these studies were cladribine, fingolimod, peginterferon beta and glatiramer acetate vs placebo and alemtuzumab vs interferon beta 1a. Three studies (ADVANCE, AFFIRM and CARE-MS I) reported no differences between groups for either the physical component summary (PCS) or mental component summary (MCS) component of the SF-36. These studies compared peginterferon beta 1a and natalizumab with placebo and alemtuzumab with interferon beta 1a. The CONFIRM study reported a greater improvement in PCS with glatiramer acetate than with placebo ($p<0.05$) but found no difference for MSC. OPERA I reported no difference in change from baseline in PCS between ocrelizumab and interferon beta 1a ($p=0.22$), while OPERA II found a greater improvement in PCS with ocrelizumab compared to placebo ($p=0.04$).

A further four studies provided data on QoL but did not use the standard EQ-5D or SF-36 specified as in scope for this appraisal. The used the MSQoL-54[106] (GOLDEN, PEGINTEGRITY), MSIS-29 (ASSESS)[107] and a 0-100 VAS to measure global wellbeing VAS (Saida 2017).

5.1.7 Summary

Table 10 provides an overview of the results for each outcome in the general RRMS population. For each outcome, it provides a summary of the number of studies that contributed to the synthesis, the number of interventions included in the synthesis and any interventions for which data were not available for this outcome, the most and least effective interventions, and any information available on the comparison of natalizumab biosimilar and natalizumab, or where data were not available on natalizumab biosimilar we summarise evidence on natalizumab compared to placebo.

Figure 16 Forest plot of hazard ratio (HR) and 95% credible intervals for time to developing at least one adverse event (fixed effects NMA; RRMS population).

Blue lines indicate result from the NMA, green lines indicate results from direct evidence and purple lines from indirect evidence. P-values relate to comparisons between direct and indirect evidence. Note that the indirect evidence lines are only included if there is also direct evidence

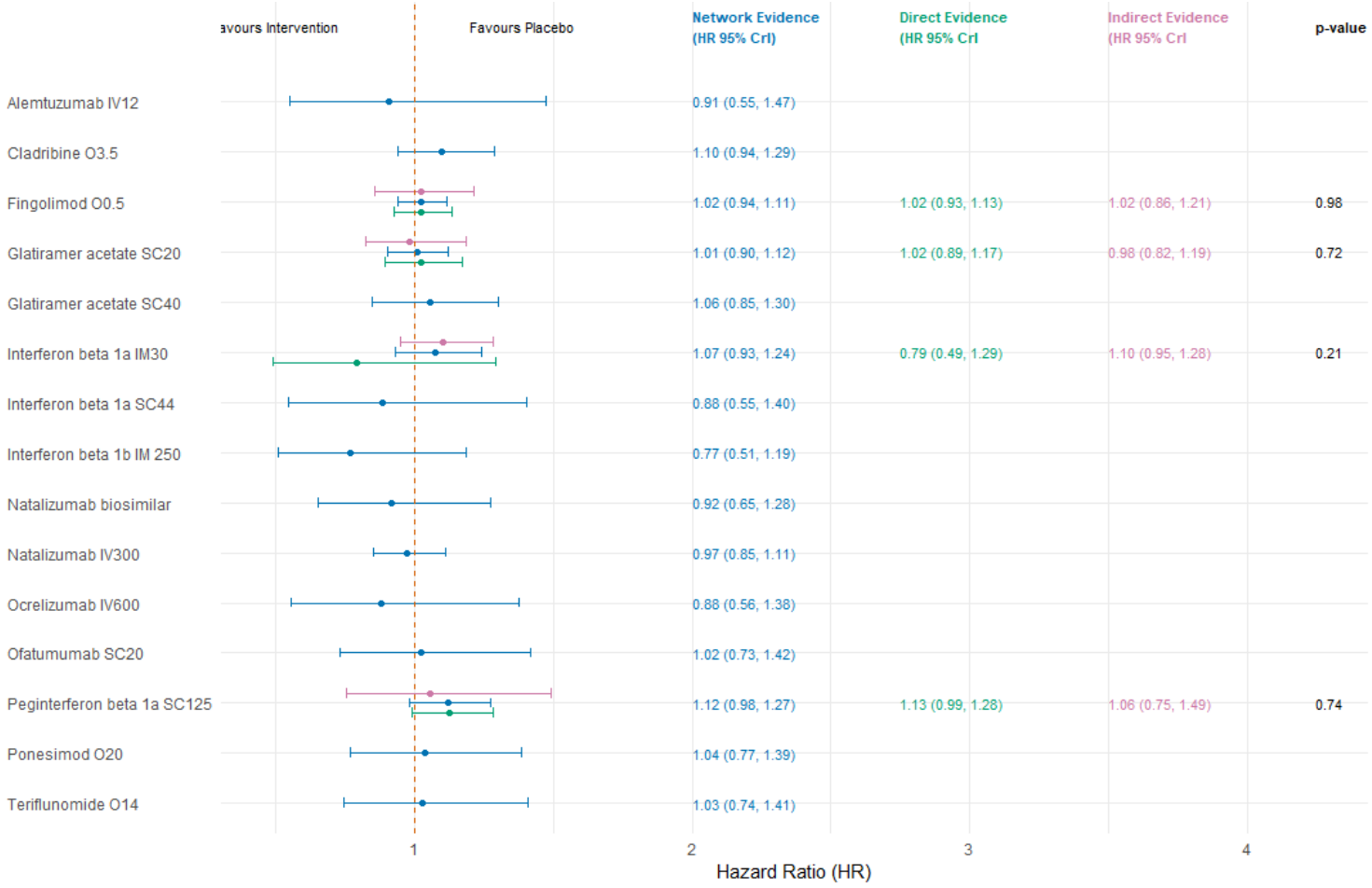


Figure 17 Forest plot of hazard ratio (HR) and 95% credible intervals for time to developing at least one serious adverse event (fixed effects NMA; RRMS population).

Blue lines indicate result from the NMA, green lines indicate results from direct evidence and purple lines from indirect evidence. P-values relate to comparisons between direct and indirect evidence. Note that the indirect evidence lines are only included if there is also direct evidence

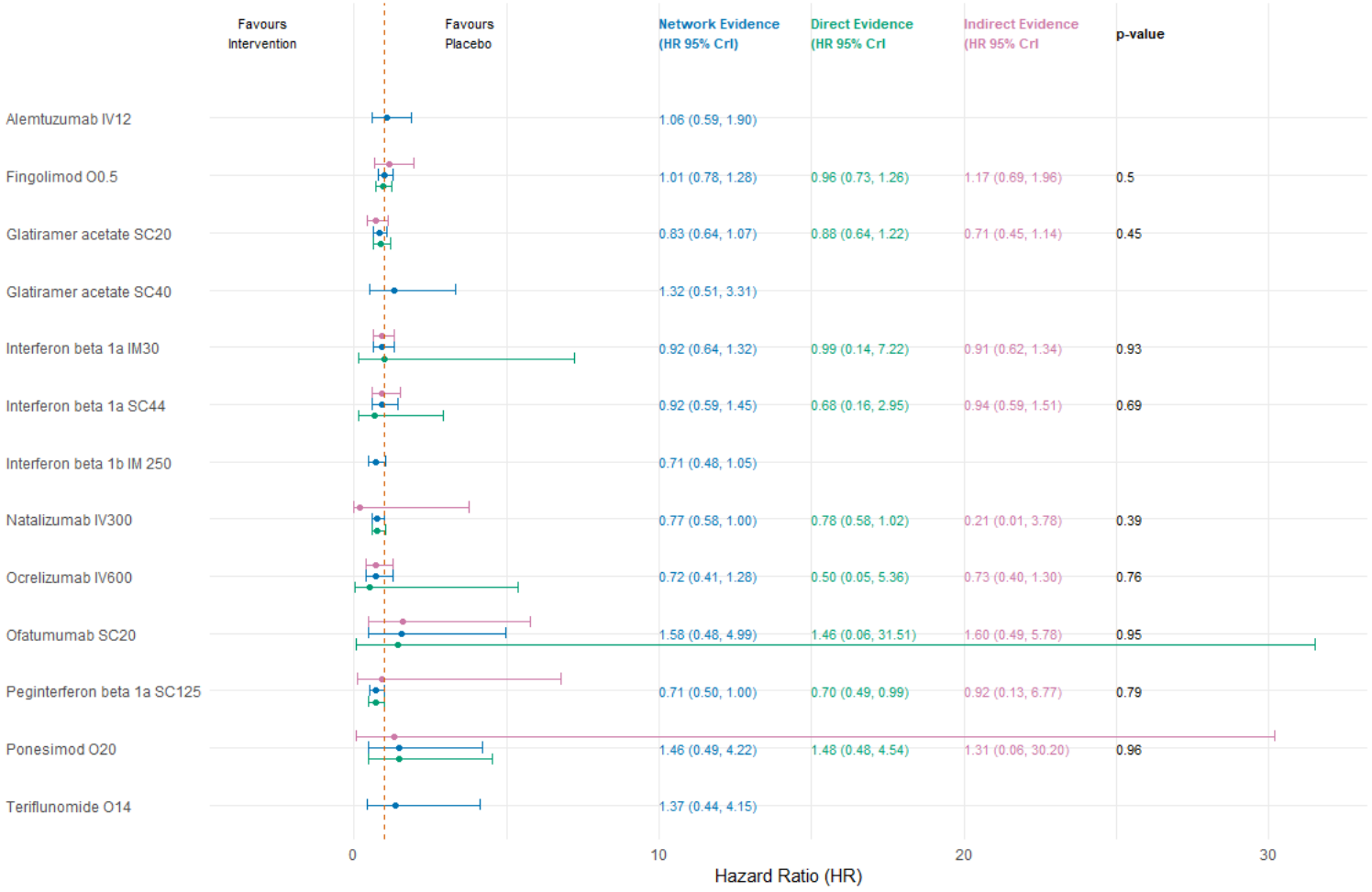


Figure 18 Forest plot of hazard ratio (HR) and 95% credible intervals for time to treatment discontinuation (fixed effects NMA; RRMS population).

Blue lines indicate result from the NMA, green lines indicate results from direct evidence and purple lines from indirect evidence. P-values relate to comparisons between direct and indirect evidence. Note that the indirect evidence lines are only included if there is also direct evidence

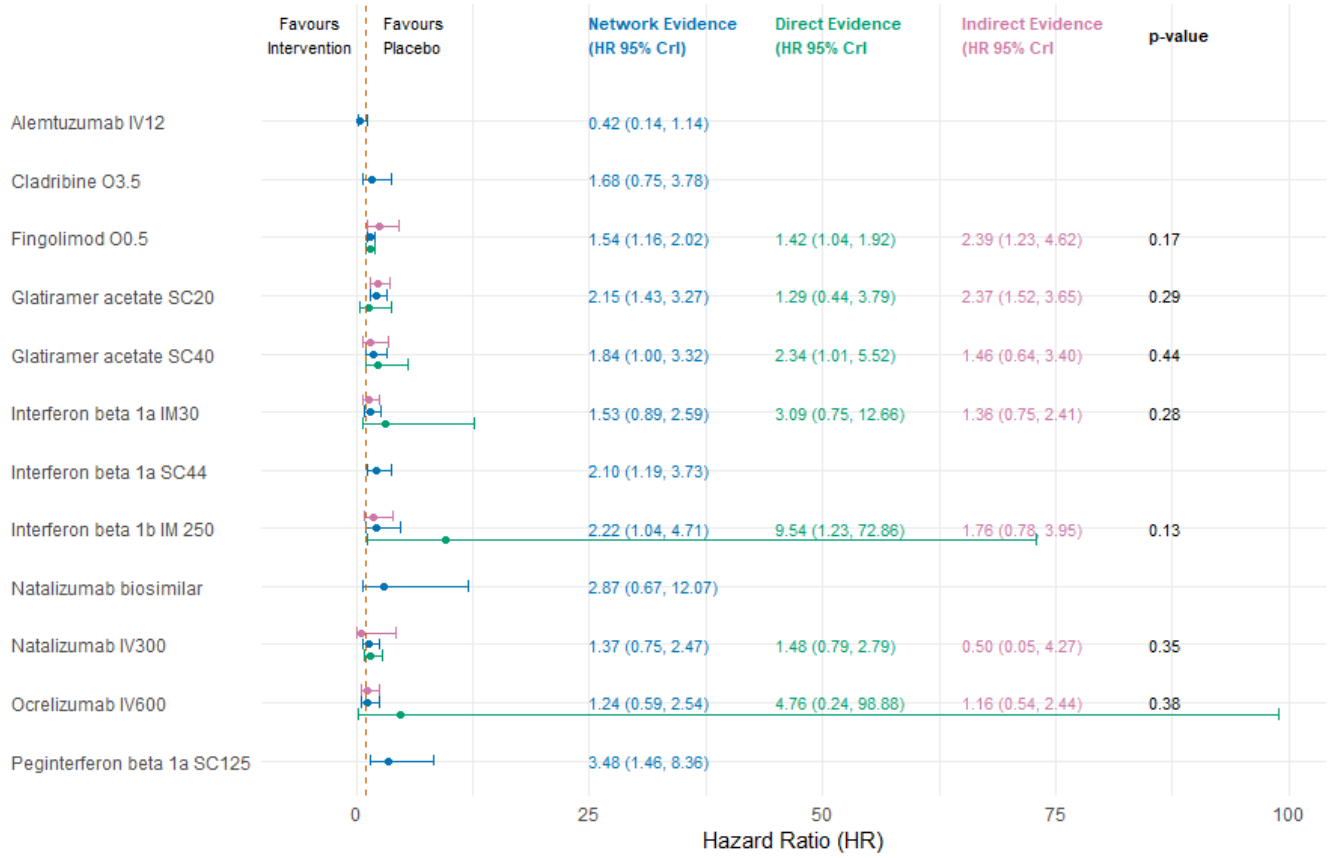


Table 10 Summary of results for each outcome evaluated in the RRMS studies

Outcome	Number of studies (participants)	Number of interventions in network	Interventions excluded from network/synthesis	Most effective interventions	Least effective interventions	Data on Natalizumab and Natalizumab biosimilar
ARR	39 (20, 810)	17	AHSCT	Alemtuzumab, natalizumab and ocrelizumab	Interferon beta, glatiramer acetate, ponesimod, teriflunomide	Natalizumab vs natalizumab biosimilar: RR 0.65 (95% CI 0.33, 1.23)
CDP3	15 (10, 635)	12	AHSCT, teriflunomide, ponesimod, ofatumumab, natalizumab biosimilar, glatiramer acetate SC40	Alemtuzumab, cladribine, fingolimod, natalizumab, ocrelizumab, interferon beta 1a (SC22 & 44) and peginterferon beta 1a	Other interferon beta and glatiramer acetate	Natalizumab vs placebo HR 0.58 (0.43, 0.76)
CDP6	14 (9,306)	11	AHSCT, teriflunomide, ponesimod, ofatumumab, natalizumab biosimilar, glatiramer acetate SC40, interferon beta 1a SC22	Alemtuzumab, fingolimod, natalizumab ocrelizumab, interferon beta 1b and peginterferon beta 1a	Other interferon beta, glatiramer acetate, cladribine	Natalizumab vs placebo: HR 0.46 (0.33, 0.63)
MRI Gd+	19 (10, 562)	11	AHSCT, ofatumumab, interferon beta 1a (SC22), glatiramer acetate (SC40), ponesimod, teriflunomide, peginterferon beta 1a	Alemtuzumab, cladribine, fingolimod, natalizumab, natalizumab biosimilar, ocrelizumab, interferon beta 1b	Interferon beta 1a and glatiramer acetate	Natalizumab vs natalizumab biosimilar: HR 1.29 (0.69, 2.37),
MRI T2	17 (8,883)	12	AHSCT, ofatumumab, glatiramer acetate (SC40), ponesimod, teriflunomide, peginterferon beta 1a	Alemtuzumab, cladribine, fingolimod, natalizumab, natalizumab biosimilar, ocrelizumab, interferon beta 1b	Interferon beta 1a and glatiramer acetate	Natalizumab vs natalizumab biosimilar: HR 1.07 (0.73, 1.57)
AEs: Any	24 (16, 673)	16	AHSCT, interferon beta 1a (SC22),	No evidence of a difference between interventions		Natalizumab vs natalizumab biosimilar: HR 1.07 (0.73, 1.57)

Outcome	Number of studies (participants)	Number of interventions in network	Interventions excluded from network/synthesis	Most effective interventions	Least effective interventions	Data on Natalizumab and Natalizumab biosimilar
AEs: SAE	30 (18, 748)	14	AHSCT , iterferon beta 1a (SC22), cladribine, natalizumab biosimilar	No evidence of a difference between interventions		Natalizumab vs placebo: HR 0.77 (0.58, 1.00)
AEs: Treatment discon-tinuation	29 (17, 892)	13	AHSCT, ofatumumab, interferon beta 1a (SC22), ponesimod, teriflunomide	No evidence of a difference for all other interventions	Fingolimod, glatiramer acetate, interferon beta 1a (SC44), interferon beta 1b, & peginterferon beta 1a	Natalizumab vs natalizumab biosimilar: HR 0.48 (0.13, 1.76)
Treatment related AEs	8 (3,361)	7	All except: Peginterferon beta 1a, natalizumab, natalizumab biosimilar, ofatumumab, glatiramer acetate, interferon beta 1a, ocrelizumab	No evidence of a difference between interventions		Natalizumab vs natalizumab biosimilar: RR 1.11 (0.56, 1.46)
Quality of Life	8	4	All except: cladribine, fingolimod, peginterferon beta and glatiramer acetate	Little evidence of any effect on QoL		No data

5.2 Highly active MS (HARRMS) population

Eight studies (2,097 participants) reported data on patients with HARRMS. Two of these studies (CARE-MS II[71] and MIST[72]) were conducted exclusively in patients with HARRMS the others were conducted in the general RRMS population but reported results separately for the highly active population. For OPERA I & II[67] and for FREEDOMS and FREEDOMS II[73], results were only available for the two studies combined – we therefore consider these as single studies in this section. None of the studies evaluated natalizumab or natalizumab biosimilar, the technologies of interest for this appraisal. However, one of the studies that compared natalizumab with placebo was conducted in a population where participant were required to have had at least one relapse in the previous year and a very high proportion of participants (88%) had previously been treated with a DMT (IFN beta 1a, IFN beta 1b, azathioprine, or fingolimod) – this was close to the definition that we set in section 4.3.6 of at least 90% having highly active disease. This study was conducted exclusively in Japanese patients. We included this study in the analysis for the HARRMS population as the best available evidence. However, this study only reported data on ARR and AEs.

Table 5 provides an overview of the interventions evaluated by the included studies. Interventions evaluated in the HARRMS included: fingolimod, ocrelizumab, alemtuzumab, and cladribine with Saida 2017 evaluating natalizumab. Two studies included a placebo control group, four studies included beta-interferon as the comparator and one compared AHSCT to a DMT as chosen by the investigators.

Table 46 (Appendix 3) provides a summary of the baseline characteristics of participants included in the HARRMS studies. OPERA I/II[67] did not report baseline characteristics separately for the HARRMS population. For the other studies, mean age ranged from 35 to 39 years (median 37 years – similar to the overall RRMS population), the proportion of female participants ranged from 62 to 76% (median 69%, also similar to the overall RRMS population), baseline EDSS score from 1.0 to 3.5 (median 2.7 – slightly higher than overall RRMS), baseline annual relapse rate was only reported for CARE-MS II and FREEDOMS II and ranged from 1.5 to 1.7 (lower than RRMS population), and mean disease duration at baseline ranged from 4.5 to 7 years (median 6.2 years), ethnicity was not reported in these studies. All participants had received previous treatment with DMTs – the actual treatments varied across studies but generally included interferon beta 1a, interferon beta 1b, and glatiramer acetate. Publication years ranged from 2010 to 2019.

Definitions of highly active disease varied across studies – all required previous treatment with DMT, some definitions specified that this should have been either interferon beta or glatiramer acetate others did not specify which treatments. Studies also included requirements for relapses in the previous year, despite treatment, but the specific requirements varied across studies from at least one relapse in the previous year with MRI evidence of progression, at least the same number of relapses in the previous year as in the previous 2 years or the preceding year.

5.2.1 Risk of bias

Table 11 provides a summary of the risk of bias assessment for studies in the HARRMS population, stratified according to outcome. Results tables in Appendix 4 also include the overall risk of bias for each study for each outcome evaluated. All studies had the same overall risk of bias judgement for all outcomes; three (CARE-MS II, MIST and FREEDOMS I/II) were judged at high risk of bias – in CARE-MS II and MIST participants were aware of treatment allocation, and in FREEDOMS II there was a large proportion of missing data which was considered potentially related to the outcome. The CLARITY study was judged at some concerns as there was missing data, but all randomised participants were included in the analysis. The other two studies in the HARRMS population (FREEDOMS and TRANSFORMS) and Saida 2017 were judged at low risk of bias.

5.2.2 Annualised Relapse Rate (ARR)

All studies except MIST reported data on ARR. The studies did not create a connected network, but by assuming a class effect for the two different interferon beta 1a comparators (IM30 and SC44) and combining these into a single node we were able to create a connected network.

We therefore included six studies (2,162 participants) evaluating seven interventions in the NMA for ARR in the highly active population. The network geometry for this analysis is shown in Figure 19. The placebo group served as the reference group throughout. The DIC for the fixed effects model was similar to that for the random effects model (16.2 vs 16.1) (Table 88). The residual deviance was very similar for both fixed and random effects (8.1 vs 8.0 on 8 data points) and indicated good fit for both models. The heterogeneity standard deviation estimated by the random effects model (tau (95% CrI) of 1.40 (0.05, 3.95) in Table 59) was high when compared to the average treatment effect on the log rate ratio scale (-0.58 in Table 59) but its 95% CrI were wide suggesting limited evidence to estimate it, thus supporting the use of fixed effects. We therefore present results for the fixed effects model for this outcome. Figure 38 (Appendix 5) shows very good fit for each study to the NMA model.

Figure 19 Network plot for NMA for ARR (highly active population)

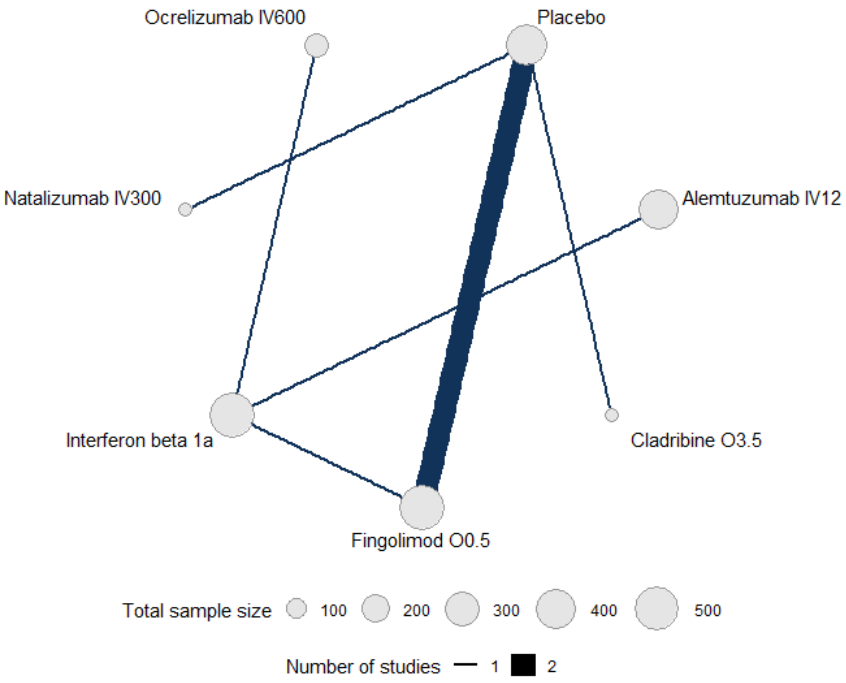
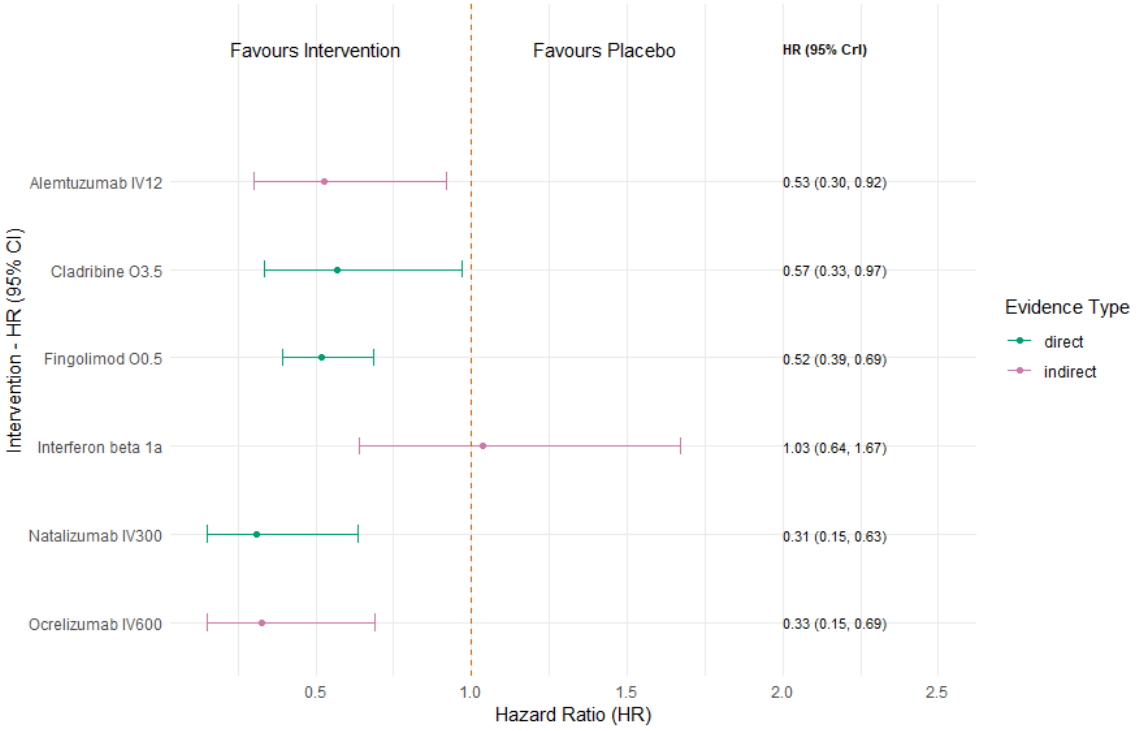


Figure 20 shows the rate ratio (RR) and 95% credible intervals (CrI) for comparison of each intervention included in the network with placebo. All interventions with the exception of interferon beta 1a were associated with a greater reduction (i.e., RR<1 AND 95% CrI excluding 1.00) in the risk of relapses compared to placebo. Results were similar for both random and fixed effects models, although credible intervals were very wide from random effects models (Table 88 in Appendix 5). The ranking of interventions and the probability that each intervention would be ranked first is shown in Table 8, with Table 90 (Appendix 5) showing the probability that each intervention will rank in a specific position. Ocrelizumab and natalizumab had the highest mean rankings (both 1.8 (95 CrI 1, 5)) with Natalizumab having a higher probability of ranking first (53% vs 44%). All other interventions in the network had ≤2% probability of ranking first. Table 89(Appendix 4) shows the RR (95% CrI) for each intervention pair comparison evaluated in the NMA.

Figure 20 Forest plot of rate ratios (RR) and 95% credible intervals from fixed effects NMA for ARR (fixed effects NMA; HA population).
Green lines indicate results from direct evidence and purple lines from indirect evidence.

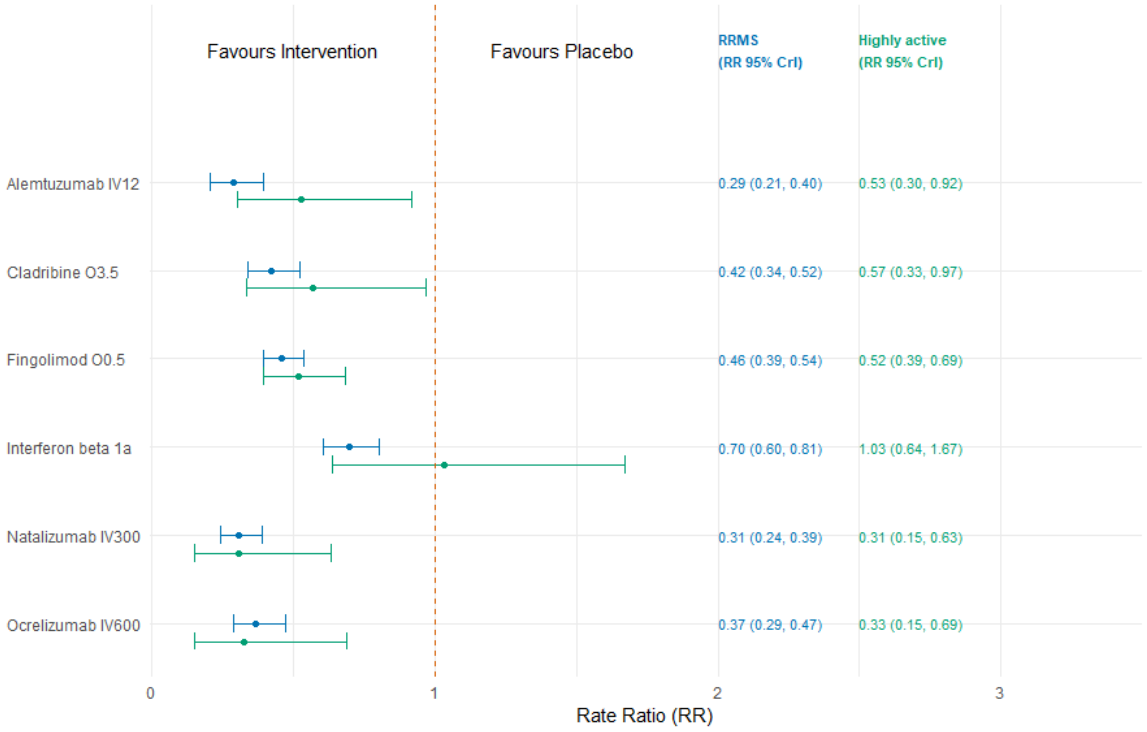


Comparison of ARR results between highly active and RRMS population

As we only had data on a limited number of interventions in the highly active population, we conducted an ad hoc analysis to determine whether there was any evidence of a difference in the relative effectiveness of interventions in the highly active and RRMS population. To allow direct comparisons between populations, we conducted a sensitivity analysis in the RRMS population where we restricted the network to the seven interventions in the network for ARR in the highly active population. As we had combined the interferon beta 1a interventions into a single node for the highly active population, we did the same for the RRMS population. Figure 21 shows that estimates of RR for ARR derived from the two different MS populations were very similar, although 95% credible intervals were wider in the highly active population. This would be expected as fewer studies contributed to these estimates.

Figure 21 Forest plot of rate ratios (RR) and 95% credible intervals from NMA for ARR in the highly active and RRMS populations (fixed effects NMA)

Blue lines indicate results in the general RRMS population and green lines in the highly active population



5.2.3 Disease progression

All studies except TRANSFORMS and Saida 2017 reported data on disease progression. Two studies reported data for CDP3 (CLARITY, FREEDOMS and OPERA I/II) and five reported data for CDP6 (CARE-MS II, CLARITY, FREEDOMS I/II, OPERA I/II and MIST). We could not create a connected network for either disease progression outcome and so a NMA was not performed. Results from these studies, including HRs and 95% CIs, are reported in Table 12. All interventions (alemtuzumab, cladribine, fingolimod, ocrelizumab and AHSCT) were associated with a reduced risk of disease progression confirmed at both 3 and 6 months compared to comparator interventions (interferon beta 1a, placebo or iDMT). To allow comparison of the effect in the highly active population and the general RRMS population we also included data from these studies in the RRMS population in Table 12. There were no clear differences in effect between the highly active or general RRMS population for disease progression, although HR estimates tended to be slightly lower (i.e. suggesting greater effect) in the highly active population, 95% CIs were wide and overlapped with those from estimates from the general RRMS population.

5.2.4 MRI outcomes

CARE-MS II was the only study to report data on MRI outcomes in the HARRMS population. This study reported that alemtuzumab was associated with a lower risk of both Gd+ lesions (RR 0.40, 95% CI 0.27, 0.60) and new or enlarging T2 lesions (RR 0.68, 95% CI 0.59, 0.79) than beta interferon 1a. The related CARE-MS I study, which was conducted in the general RRMS population, reported similar results - alemtuzumab was associated with a lower risk of both Gd+ lesions (RR 0.37, 95% CI 0.23, 0.60) and new or enlarging T2 lesions (RR 0.84, 95% CI 0.71, 0.99) than beta interferon 1a.

5.2.5 Adverse events

CARE-MS II was the only study to report data on adverse events specifically in the HARRMS population. Data on adverse event were also available for Saida 2017 – these are included in the analysis for the general RRMS population and suggest fewer AEs in the Natalizumab arm compared to placebo, although with no strong evidence of a difference between groups. CARE-MS II reported that alemtuzumab was associated with a very small increased risk of any adverse event (RR 1.04, 95% CI 1.00, 1.08) but a lower risk of treatment discontinuation (RR 0.43, 95% CI 0.21, 0.88) than beta interferon 1a. There was no difference in the risk of serious AEs (RR 0.83, 95% CI 0.67, 1.04). Comparison with the related CARE-MS I study suggested similar results for serious AEs (RR 0.79, 95% CI 0.52, 1.18). However, there was a very small decreased risk of any adverse event (RR 0.94, 95% CI 0.90, 0.99) and a large increased risk of treatment discontinuation (RR 4.42, 95% CI 1.56, 12.55) for alemtuzumab compared to beta interferon 1a. Both CARE-MS I and II were judged at high risk of bias.

5.2.6 Quality of life (QoL)

CARE-MS II and MIST were the only studies to report data on adverse events in the highly active MS population. Both studies were judged at high risk of bias. MIST reported that QoL was better in those treated with AHCT compared to those in the comparator DMT group ($p<0.001$). CARE-MS II found no difference between groups in the SF-36 MCS score, but a significantly greater improvement with alemtuzumab on the PCS score compared to interferon beta 1a. The related CARE-MS I study, conducted in the general RRMS population, found no difference in QoL between intervention groups.

Table 11 Risk of bias for studies in the HARRMS population

Study	Outcome	Domain					Overall	Rationale
		1	2	3	4	5		
CARE-MS II[71]	ARR; MRI; AE; QoL	Low	High	Some concerns	Low	Low	**High**	Patients and carers were aware of the treatment assignments; missing outcome data but sensitivity analyses performed
CLARITY[86]	ARR; CDP	Low	Low	Some concerns	Low	Low	**Some concerns**	Some missing data potentially related to outcome but all randomised participants included in analysis
FREEDOMS 1/II[108]	ARR; CDP	Low	Low	High	Low	Low	**High**	Large proportion of missing data potentially related to outcome
MIST[72]	CDP	Some concerns	High	Low	Low	Low	**High**	Patients and carers were aware of the treatment assignments
	QoL					Some concerns		QoL not specified as outcome in trial registry entry - only outcome specified was disease progression
OPERA I/II[67]	ARR; CDP	Low	Low	Low	Low	Low	**Low**	No concerns
Saida 2017[79]	ARR; AE	Low	Low	Low	Low	Low	**Low**	No concerns
TRANSFORMS[75]	ARR; CDP; AE	Low	Low	Low	Low	Low	**Low**	No concerns

Domain 1: Risk of bias arising from the randomization process; Domain 2: Risk of bias due to deviations from the intended interventions; Domain 3: Risk of bias due to missing outcome data; Domain 4: Risk of bias in measurement of the outcome; Domain 5: Risk of bias in selection of the reported result

ARR: annualised relapse rate; CDP: confirmed disease progression; AE: adverse event; QoL: Quality of Life

Table 12 Estimates of HR and 95% CIs for disease progression confirmed at 3 (CDP3) and 6 (CDP6) months in the highly active and general RRMS populations from studies that reported data in people with HARRMS

Study Name	Intervention	Comparator	Follow-up (mths)	HARRMSpopulation		General RRMS Population	
				CDP3: HR (95% CI)	CDP6: HR (95% CI)	CDP3: HR (95% CI)	CDP6: HR (95% CI)
CARE-MS II[71] (HA) & CARE-MS I (RRMS)	Alemtuzumab	Interferon beta 1a (SC44)	24	NR	0.58 (0.38, 0.87)	NR	0.70 (0.40, 1.23)
CLARITY[86]	Cladribine	Placebo	24	0.25 (0.07, 0.89)	0.20 (0.04, 0.91)	0.67 (0.48, 0.93)	NR
FREEDOMS[74]	Fingolimod	Placebo	24	0.59 (0.29, 1.20)	0.50 (0.34, 0.90)	0.70 (0.52, 0.96)	1.59 (1.11, 2.27)
FREEDOMS II[73]	Fingolimod	Placebo	24	NR		0.83 (0.61, 1.12)	0.72 (0.48, 1.07)
OPERA II[67]	Ocrelizumab	Interferon beta 1a (SC44)	24	0.47 (0.23, 0.95)	0.50 (0.23, 1.09)	0.57 (0.37, 0.9)	0.57 (0.34, 0.95)
OPERA II[67]						0.63 (0.42, 0.92)	0.63 (0.40, 0.98)
MIST[72]	AHSCT	iDMT	34	NR	0.07 (0.02, 0.24)	NA	

6 Assessment of cost effectiveness

Sections of this Chapter have been reproduced from the study's Protocol document, available at the NICE website.[1]

6.1 Systematic review of existing cost-effectiveness evidence

We conducted a review to summarise evaluations of the cost effectiveness of interventions for highly active relapsing-remitting multiple sclerosis after at least one disease modifying therapy and to identify studies/evaluations reporting UK costs data to inform the model. The review followed the principles outlined in the Centre for Reviews and Dissemination (CRD) guidance for undertaking reviews in health care and the NICE Health Technology Evaluations Manual.[46, 47] The review is reported according to the PRISMA 2020 guidance [48]

6.1.1 Study identification

On the 15th May 2024, we searched:

- MEDLINE (MEDALL) 1946 to May 14, 2024;
- Embase 1974 to 2024 May 14;
- Econtlit 1981-current; and
- NHS Economic Evaluations Database (NHS EED) via https://www.crd.york.ac.uk/CRDWeb/HomePage.asp.

Economic evaluations identified by the clinical effectiveness searches were flagged by the reviewers for potential inclusion in the review of economic models.

6.1.2 Selection criteria

Studies were selected by two researchers if they reported an:

- economic evaluation in HARRMS; OR
- economic evaluation or costs study in RRMS if done in the UK.

We excluded evaluations where the focus was on the perspectives of payers in countries other than the UK to align our review to the needs of NICE decision-makers.

6.1.3 Results

A flowchart detailing the study identification and selection process is reported in Figure 22. Table 13 provides an overview of the studies included in the review. Studies excluded at full text are reported in Table 42 with reasons for exclusion. We identified seven evaluations (in eight reports). The review (in particular the studies by Noon and Montgomery),[109, 110] and review of NICE TAs, highlighted that DES, rather the Markov multistate modelling, is a suitable way to model disease progression for cost-effectiveness analysis in RRMS.

Figure 22 PRISMA flowchart for systematic review of economic evaluations

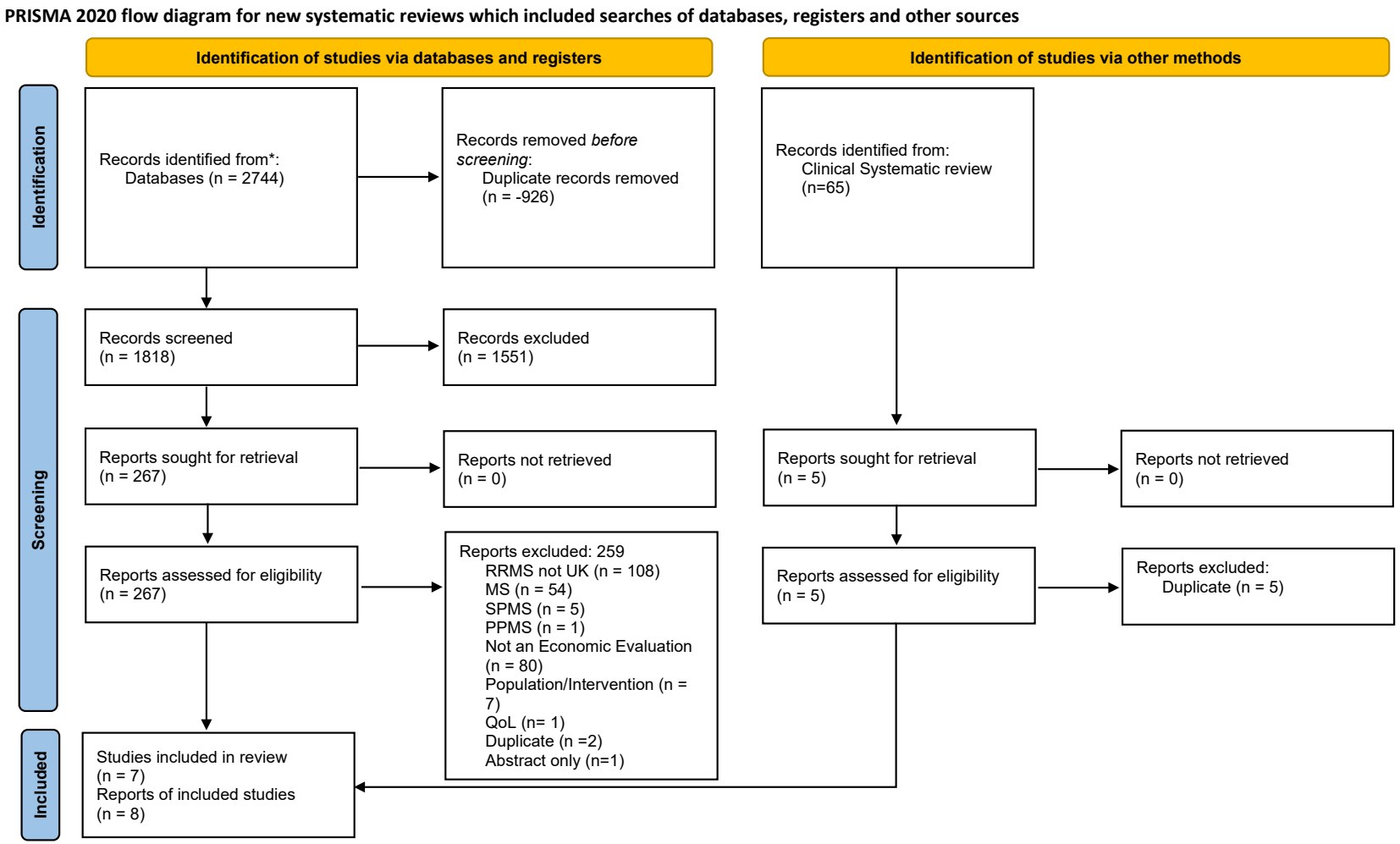


Table 13 Studies included in the systematic review of economic evaluations

Study	Aim	Model type and perspective	Population	Data inputs	Time horizon and discount
Spelman[111]	To evaluate clinical and cost-effectiveness of natalizumab and fingolimod	Markov Model (annual cycle length). NHS perspective.	Adults (>18) with RES - RRMS (≥2 relapses in prior year) starting treatment with natalizumab, fingolimod, or BRACETD, or were previously naïve to DMTs or treated with a different BRACETD.	Clinical IPD from MSBase Registry[112] • ARR • TtfR • CDW6M • CDI6M Costs UK MS burden of illness study[113] • Annualised acquisition, administration and monitoring (UK list price). • Direct and indirect (edss0-9) • Relapse (direct). • Adverse Events. Utilities UK MS burden of illness study[113] • RRMS (EDSS 0-9) • SPMS (EDSS 0-9) • Caregiver • Relapse • Adverse events	Lifetime Horizon. Discount Rate:3.5%
Noon[109]	To investigate the impact of economic model type on the cost-effectiveness of disease-modifying therapies (DMTs) for RRMS.	Markov and discrete event simulation (DES) models. UK payer perspective.	Adults 18-55 with HA RRMS or RES RRMS, >1 relapse in year prior and EDSS 0-5.5. (FREEDOMS[74], FREEDOMS II[114] and TRANSFORMS[75])	Clinical Natural History data from placebo arm of FREEDOMS and FREEDOMS II. EDSS >8 calculated based on London Ontario dataset.[115] • ARR Costs	Markov: baseline cohort age + 50 yrs and DES: tracked each simulated patient until death (capped at 100 yrs). Discount Rate 3.5%.

Study	Aim	Model type and perspective	Population	Data inputs	Time horizon and discount
				• Drug costs based on list price (without discount). • Resource use (administration, monitoring, AEs and drug acquisition) • Relapses (NHS National Tarif) (Costs and QALYs calculated in annual cycles with ½ cycle correction in the Markov and applied on a continuous-time basis in the DES) <u>Utilities</u> • EQ-5D • EDSS • Disutilities associated with AEs were matched across models (adverse events, retreatment).	
Hettle[116]	To assess the cost-effectiveness of cladribine tablets in HDA-RRMS compared with alemtuzumab and natalizumab	Markov (annual cycle length). NHS Perspective	Adults with RRMS, >1 relapse within 12 months, and EDSS <5.5. Based on CLARITY[86]	<u>Clinical</u> Natural History reference model using data on disability and relapse for people receiving Best Supportive Care and treatment-adjusted model combing the Natural History model with comparative efficacy and safety of treatment vs placebo.[117] • 6-months confirmed disability progression • ARR <u>Costs</u> • Drug acquisition, administration and monitoring based on list price (without discount). • Annualised direct medical costs taken from Hawton and Green[118]	50 year horizon. 3.5% discount.

Study	Aim	Model type and perspective	Population	Data inputs	Time horizon and discount
				Utilities • EDSS from CLAIRTY trial[86] • Health State Utilities from Hawton and Green.[118] • EDSS-related utility loss for caregivers.	
Melendez-Torres[119]	HTA to determine effectiveness and cost effectiveness of beta-interferon and glatiramer acetate for RRMS/SPMS.	Markov (annual cycle length). NHS and Personal and Social Services (PSS)	RRMS patients	Clinical Systematic Review and Natural History from British Columbia Multiple Sclerosis database (closed since 2009) Costs Systematic review and[120] • Resource use • Unit costs Utilities MS Trust surveys • EQ-5D converted to EQ-5D index score.	50 year horizon. 3.5% discount.
Palace[121]	To assess the long-term effectiveness and cost-effectiveness of interferon beta and glatiramer acetate.	Markov and a multilevel model (to model treatments in the RSS)	Adults >18 with 2 significant relapses in prior 2 yrs and EDSS >5.5.	Clinical UK RSS clinical cohort compared to the BCMS database. • accumulation of disability measured as EDSS progression and loss of utility.	20 years. 3.5% discount.
Herring[122]	To estimate the comparative effectiveness of switching to	Markov. UK NHS.	Adults with HA RRMS with inadequate response after >1 year on first line DMT who switched to	Clinical MSBase Registry and published trials.	Lifetime. 3.5% discount.

Study	Aim	Model type and perspective	Population	Data inputs	Time horizon and discount
	natalizumab or fingolimod or within BRACETD using real-world data and to evaluate the cost-effectiveness of switching to natalizumab versus fingolimod using a United Kingdom (UK) third-party payer perspective.		natalizumab, fingolimod, or another BRACETD. Primary endpoint: change in EDSS.	Costs/utilities: 2015 UK MS burden of illness survey used to estimate indirect costs and utility values. treatment costs were list price and standard UK costs.	
Montgomery[110, 123] (1 study in two eligible reports)	to model IPD from key trials in DES for the cost-effectiveness analysis of the treatments fingolimod and alemtuzumab recommended by NICE for use in HA RRMS patients,	DES model in C++. NHS and Personal and Social Services (PSS)	Adults 18-55 with RRMS, >1 relapse in year prior and EDSS 0-5.5. (from from FREEDOMS, FREEDOMS II and TRANSFORMS)	<u>Clinical</u> • IPD from placebo arms of HARRMS subgroup of the Key trials; FREEDOMS, FREEDOMS II and TRANSFORMS for EDSS 0-7 supplemented with data from London Ontario for EDSS >8.[17] • ARR, AEs from FREEDOMS, FREEDOMS II and TRANSFORMS. <u>Costs</u> • Drug acquisition based list price (no discount) • Treatment acquisition, administration and monitoring. • Relapse cost from NGS National Tariff • EDSS costs from previous NICE submissions[21]	Life time horizon (capped at 100). Primary output: Costs and QALYS discounted at 3.5%. ICER and NMB.

Study	Aim	Model type and perspective	Population	Data inputs	Time horizon and discount
				Utilities • EQ-5D • Disutitlties based on [9,17,21,13]	

AAR: annualized relapse rate; CDI3M: time to 3-month–confirmed disability improvement; CDI6M: time to 6-month–confirmed disability improvement; CDW3M: 3-month–confirmed disability worsening; CDW6M: 6-month–confirmed disability worsening; DES: Discrete simulation model; EDSS: Expanded Disability Status Scale; IPD: Individual Patient Data; MS: Multiple Sclerosis; QoL: Quality of Life; RES-RMMS: Rapidly Evolving Severe Relapsing-Remitting Multiple Sclerosis; RSS: Risk Sharing Scheme; SPMS: Secondary Progressive Multiple Sclerosis; SRRMS: Relapsing-Remitting Multiple Sclerosis; TtfR: time to first relapse.

6.2 Independent economic assessment

An economic model was developed to compare the cost-effectiveness of treatments for HARRMS after at least one disease modifying therapy.

The target population for our economic evaluation was people with HARRMS who have received at least one previous DMT. As the evidence on this population is limited, we used evidence in any RRMS (including studies with at least 90% of participants with RRMS) to fill any gaps.

The interventions were Natalizumab (Tysabri), delivered subcutaneously or intravenously, and intravenous natalizumab biosimilar (Tyruko). Comparators are aligned with those of the overall appraisal (Table 4):

- Glatiramer acetate
- Interferon beta 1a
- Interferon beta 1b
- Alemtuzumab
- Cladribine tablets
- Fingolimod
- Ocrelizumab
- Ofatumumab
- Ponesimod
- Autologous haematopoietic stem cell transplantation

Only comparators with efficacy and safety data, as identified by the clinical SLR, necessary for the economic model were assessed. There was no clinical evidence identified on autologous haematopoietic stem cell transplantation so this was not included in the economic model.

We aligned with recommendations of the NICE reference case. We therefore took an NHS and NHS and personal and social services (PSS) perspective and lifetime horizon. Health benefits were measured using Quality Adjusted Life Years (QALYs). Discounting was applied to both costs and benefits at the annual 3.5% rate.

The model and cost-effectiveness analysis were fully probabilistic with any specific parameter or structural sensitivity analyses also probabilistic.[124, 125]

6.3 Models used in relevant TAs

We reviewed the economic models used in relevant NICE TAs. These were the TAs for natalizumab and the comparators listed in Table 3 that were categorised as "Recommended for RRMS in specific situations or specific subtypes" or "Recommended for previously treated RRMS" in Table 3. TAs were identified by informally searching the NICE website and supplemented by any additional assessments identified by the cost-effectiveness review of Section 6.1.

6.3.1 TA767 Ponesimod

TA767 2022[42] assessed the cost-effectiveness of Ponesimod (Ponvory, Janssen) for RRMS at first or second line. The Markov model simulates a cohort of patients over a lifetime progressing through 10 RRMS & 10 SPMS EDSS health states leading up to death. The natural history of disability progression for RRMS patients was based on the British Columbia Multiple Sclerosis registry.[126] Annual relapse rates by disability[127] were based on population data from the burden of illness 2005 UK MS Survey[128] and patient data from a prospective study.[129] Conversion from RRMS to SPMS was based on data from the London Ontario MS database.[127] The placebo arm of the AFFIRM trial was used to modify the natural history for the HA RRMS subgroup.[34]

The model inputs for patients on treatment with Ponesimod were reported by OPTIMUM & OPTIMUM-LT trials. The CDP-3 & CDP-6 outcomes modify disability progression, the ARR to estimate the number of relapses, and the proportion experiencing AEs. The model accounts for treatment waning, discontinuation, and excess mortality due to MS. Health state costs[130] and utilities[128] were included. Disutilities were applied for disability, relapse, AEs, and caregivers. The External Assessment Group (EAG) was critical of the model not allowing for treatment switching or sequencing and considered this to be an oversimplification of clinical practice, they acknowledged limitations maybe due to the availability of data.

6.3.2 TA699 Ofatumumab

TA699 2021[41] assessed the cost-effectiveness of Ofatumumab (Kesimpta, Novartis) for RRMS at first or second line. The Markov model simulates a cohort of patients over a lifetime progressing through 10 RRMS & 10 SPMS EDSS health states leading up to death. The natural history of disability progression for RRMS patients was based on the British Columbia Multiple Sclerosis registry.[126] Annual relapse rates by disability[127] were based on population data from the burden of illness 2005 UK MS Survey[128] and patient data from a prospective study.[129] Conversion from RRMS to SPMS was based on data from the London Ontario MS database[127] supplemented by data from the EXPAND trial. The HA RRMS subgroup was modelled but not considered suitable for decision making.

The model inputs for patients on treatment with Ofatumumab were reported by ASCLEPIOS I & II trials. The CDP-3 & CDP-6 outcomes modify disability progression, the ARR to estimate the number of relapses, the proportion experiencing AEs, and quality of life data. The model

accounts for treatment discontinuation, and excess mortality due to MS. Health state costs were included,[130] and disutilities were applied for disability, relapse, AEs, and caregivers. The EAG was critical of the model not having incorporated loss of treatment effectiveness, they accepted treatment discontinuation as a proxy to waning as in TA533.

6.3.3 TA616 Cladribine

TA616 2019[38] assessed the cost-effectiveness of Cladribine tablets (Mavenclad, Merck Serono) for RES RRMS at first or second line and HA RRMS (SOT RRMS) at second line. The Markov model simulates a cohort of patients over a lifetime progressing through 10 RRMS & 10 SPMS EDSS health states leading up to death. The natural history of disability progression for RRMS patients from the British Columbia Multiple Sclerosis registry[126] adjusted to account for higher probability of progression on the RES and SOT subgroups using CDP-6 from CLARITY.

The model inputs for patients on treatment with Cladribine tablets were from an NMA and Meta-regression that included the key trials CLATIRY & CLARITY-EXT. The CDP-3 & CDP-6 outcomes modify disability progression, the ARR to estimate the number of relapses, the proportion experiencing AEs and quality of life data. The model accounts for treatment discontinuation, and excess mortality due to MS. Health state costs[118, 130, 131] and utilities were included,[118, 128] and disutilities were applied for disability, relapse, AEs, and caregivers. The EAG was critical of the company assuming loss of treatment effectiveness to be delayed for Cladribine tablets, they accepted treatment discontinuation as a proxy to waning to as in previous appraisals.

6.3.4 TA533 Ocrelizumab

TA533 2018[33] assessed the cost-effectiveness of Ocrelizumab (Ocrevus, Roche) for RRMS at first or second line. The multi—state Markov model simulates a cohort of patients over a lifetime progressing through 20 RRMS & 10 SPMS EDSS health states leading up to death. The natural history of disability progression for RRMS patients was based on the British Columbia Multiple Sclerosis registry.[126] Annual relapse rates by disability were based on population data from the burden of illness 2005 UK MS Survey[128] and patent data from a prospective study.[129] Conversion from RRMS to SPMS was based on data from the London Ontario MS database.[127] The placebo arm of the AFFIRM trial was used to modify the natural history for the HA RRMS subgroup.

The model inputs for patients on treatment with Ocrelizumab were reported by OPERA I & II trials. The CDP-3 & CDP-6 outcomes modify disability progression, the ARR to estimate the number of relapses, the proportion experiencing AEs and quality of life data. The model accounts for treatment discontinuation, and excess mortality due to MS. Health state costs were included,[130] and disutilities were applied for disability, relapse, AEs, and caregivers. The EAG was critical of the model not having incorporated loss of treatment effectiveness which in clinical practice would lead to patients switching on to other treatments, they accepted treatment discontinuation as a proxy.

6.3.5 TA312 Alemtuzumab

TA312 2014[39] assessed the cost-effectiveness of Alemtuzumab (Lemtrada, Sanofi) for Active RRMS at first line RES RRMS at first or second line and HA RRMS at second line. The multi-state Markov model simulates a cohort of patients over a lifetime progressing through 10 RRMS & 9 SPMS EDSS health states leading up to death. The natural history of disability progression for RRMS patients and converting to SPMS states was based on the London Ontario MS database.[127] Annual relapse rates by disability were based on population data from the burden of illness UK MS Survey[128] and patent data from two prospective studies.[129, 132]

The model inputs for patients on treatment with Alemtuzumab were from an NMAs specific to the RRMS and RES RRMS and HA RRMS subgroups that included the key trials CAMMS223, CARE-MS I & II. The Sustained Accumulation of Disability (SAD-3 & SAD-6) outcomes modify disability progression, the ARR to estimate the number of relapses, the proportion experiencing AEs and quality of life data. The model accounts for treatment discontinuation, and excess mortality due to MS. Health state costs,[130, 131, 133] were included and disutilities were applied for disability, relapse, AEs, and caregivers. The EAG was critical of the company assuming no loss of treatment effectiveness for Alemtuzumab, clinical advice was that patients would be offered alternative treatments after discontinuation but as treatment switching was not implemented in the model, the committee concluded it was appropriate to model long-term treatment waning.

6.3.6 TA254 Fingolimod

TA254 2012[40] assessed the cost-effectiveness of Fingolimod (Gilenya, Novartis) for HA RRMS at second line. The Markov model simulates a cohort of patients over a lifetime progressing through 10 RRMS & 10 SPMS EDSS health states leading up to death. The natural history of disability progression for RRMS patients and converting to SPMS states was based on the London Ontario MS database.[115] Annual relapse rates by disability were based on population data from the burden of illness UK MS Survey[128] and patient data from a prospective study.[129]

The model inputs for patients on treatment with Fingolimod versus Avonex were reported on the TRANSFORMS & FREEDOMS trials. An NMA was undertaken to estimate relative treatment effects of other beta interferons. The SAD-3 & SAD-6 outcomes modify disability progression, the ARR to estimate the number of relapses, the proportion experiencing AEs. The model accounts for treatment discontinuation, and excess mortality due to MS. Health state costs,[34] utilities[128], were included and disutilities were applied for disability, relapse, AEs, and caregivers. The model has many limitations which were critiqued by the EAG and are summarised in Table 92, they called for a new decision model, one that better reflects clinical practice in future appraisals of Multiple Sclerosis.

6.3.7 TA127 Natalizumab

TA127 2007[34] assessed the cost-effectiveness of Natalizumab (Tysabri, Biogen Idec) for RES RRMS at first or second line. The multi-state Markov model simulates a cohort of patients over a lifetime progressing through 10 RRMS & 10 SPMS EDSS health states leading up to death. The natural history of disability progression for RRMS patients and converting to SPMS states was based on the London Ontario MS database.[115] Annual relapse rates by disability were based on population data from the burden of illness UK MS Survey[128] and patient data from a prospective study.[129] The placebo arm of the AFFIRM trial was used to modify the natural history for the HA RRMS subgroup.

The model inputs were obtained from a number of sources. The Hazard ratios for disability progression and annual relapse of RES RRMS patients on treatment with Natalizumab was obtained from the AFFIRM trial and converted to risk ratios. The risk ratios for disability progression and annual relapse for patients on beta interferon or glatiramer acetate were obtained from pairwise meta-analyses, data from two Cochrane reviews.[134, 135] The analyses derived relative treatment effects contrasting the risk ratios from the Intention to Treat (ITT) and RES Natalizumab groups versus either of the beta interferon or glatiramer acetate ITT groups' risk ratios. The risk ratios for disability progression could be multiplied directly with the natural history transition matrices. However, the relapse risk ratios describe had to be transformed into relative relapse rates using the annualised relapse rate from the placebo groups in AFFIRM from the RES RRMS sub group, and the ITT main group as a proxy for the SOT RRMS subgroup. Health state costs and utilities[128], were included and disutilities were applied for disability, relapse, AEs, and caregivers. The ERG was critical of the company excluding the SENTINEL trial SOT RRMS subgroup data from the model, especially that it was relied on for the marketing authorisation.

6.3.8 Common criticisms

1. Treatment sequencing and variable treatment waning was an issue in all the reviewed submissions (TA767, TA699, TA616, TA533, TA312, TA254 and TA127) to varying degrees. These TAs explain that clinical practice is to switch patients to alternative treatments if their current drug is no longer effective. The ERGs have accepted treatment discontinuation as proxy for loss of effectiveness over time, despite lack of evidence on waning from the key trials. This is because treatment switching was not modelled in any of these submissions.

2. Previous models (TA767) have modelled relative risk of death being applied to each EDSS health state, taken from Pokorski (1997) which demonstrated that risk of death because of multiple sclerosis was primarily dependent on disability. But this dataset is quite old and has been criticised by clinicians for this reason.

3. Previous models in Multiple sclerosis have had limited ability to accurately reflect the course of the condition. In TA767 and TA699 an implausible number of patients were found in high EDSS states contrary to what would be observed in clinical

practice. In TA699 and TA127 issues with converting from RRMS to SPMS were discussed. In TA254 and TA127 issues with unrealistic disability progression when treatment effects were applied to the natural history was discussed.

6.4 Model structure

To overcome the key criticisms of the previous manufacturer models for RRMS submitted to NICE (Section 6.3.8), we adopted an individual-level discrete-event simulation (DES) model.[136] This makes it possible to model treatment sequences and enable treatment-specific waning patterns. The inflexibility of cohort Markov models made it difficult to accurately reflect the course of MS, leading to implausible numbers of patients in the high EDSS states.[42] The flexibility of DES better reflects the natural course of MS, and eases the inclusion of new standardised mortality rates by EDSS (TA767).[42, 137]
Our model structure was influenced by the recent Dutch clinical guidelines models on RRMS which was a microsimulation accounting for treatment sequences. [138-141] However, rather than using a DES, this microsimulation used an underlying multistate structure defined by EDSS and SPMS status, similar to the Markov models used in previous NICE submissions (Section 6.3). Our justification for adopting event-based rather than state-based modelling is that the target of RRMS treatment is to reduce the events of relapse and disability progression, rather than to directly affect EDSS severity or SPMS status. A DES is therefore better tailored to RCT data and the focus of RRMS treatment.

The model is illustrated in Figure 23. The attributes of the DES represent important demographic and disease characteristics. The modelled disease characteristics included EDSS ($\in$ (0, …, 9)) and SPMS status to thus capture health state information of the previous RRMS Markov models (Section 6.3). Age and gender were modelled as demographic attributes and determine the rate of background mortality. Treatment status was included and described in more detail below.

Event rates depended on some or all of these attributes. If a patient has not yet progressed to SPMS, events included increase in severity (i.e., EDSS increase), decrease in severity (i.e., EDSS reduction), progression to SPMS, relapse, adverse events, treatment change not driven by an event, and death. If a patient has progressed to SPMS, the events included increase in severity (i.e., EDSS increase), relapse, adverse events, and death.

Treatment status is a key attribute, and the sequence of treatment is represented in Figure 24. The initial treatment was any of the interventions/comparators in highly active RRMS. Following this, rescue therapy and later line therapy will follow the currently recommended pathway described in Section 1.3.5. Patients can progress to SPMS on any line of RRMS therapy and are then assumed to receive an average 'basket' of approved therapies, as described in Section 1.3.5.

We resolved competing risks using the "event-specific" approach, which requires sampling times for all competing events and simulating the event that is the first to occur.[142, 143] The

alternatives (sampling the event to occur first and then the time-to-event; sampling the time-to-event and then the event) required data to be analysed in a joint manner, which was not possible in this setting as rates of (for example) CDP3/6, ARR, and adverse events were estimated independently.

Progressive Multifocal Leucoencephalopathy (PML) is an important side effect of some MS drugs, particularly natalizumab and its biosimilar.[76, 144] It is caused by suppression of the immune system which can cause the John Cunningham human polyomavirus (JCV), to become active.[144] Biogen, the manufacturer of natalizumab, currently fund JCV testing and report a risk of PML.[145] However, our clinical advice was that this scheme is not widely implemented so the cost of JCV testing was included for natalizumab. Testing is also not routinely done for the biosimilar and would need to be funded by the NHS. We therefore included this JCV virus testing for the biosimilar in the base case .

Figure 23 Model diagram for cost-effectiveness DES model

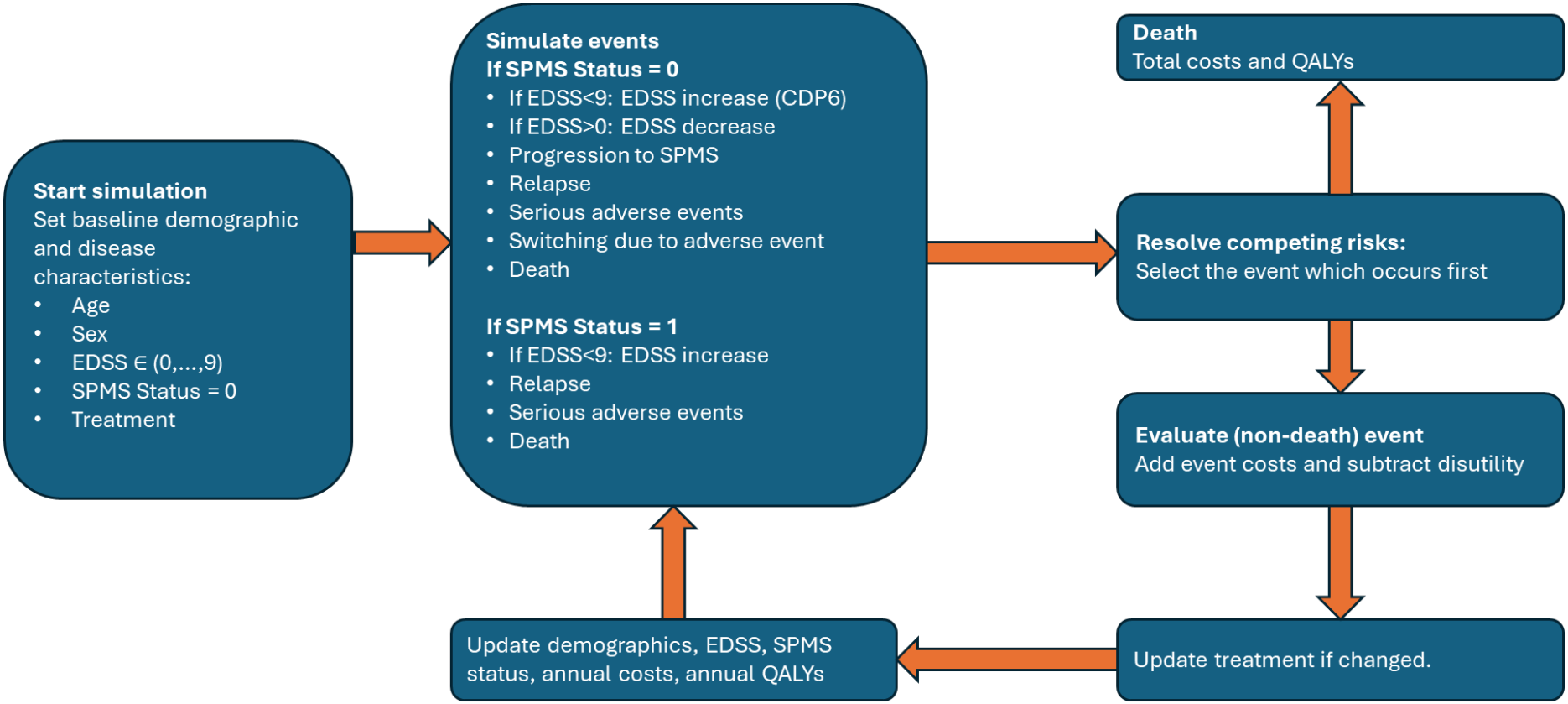
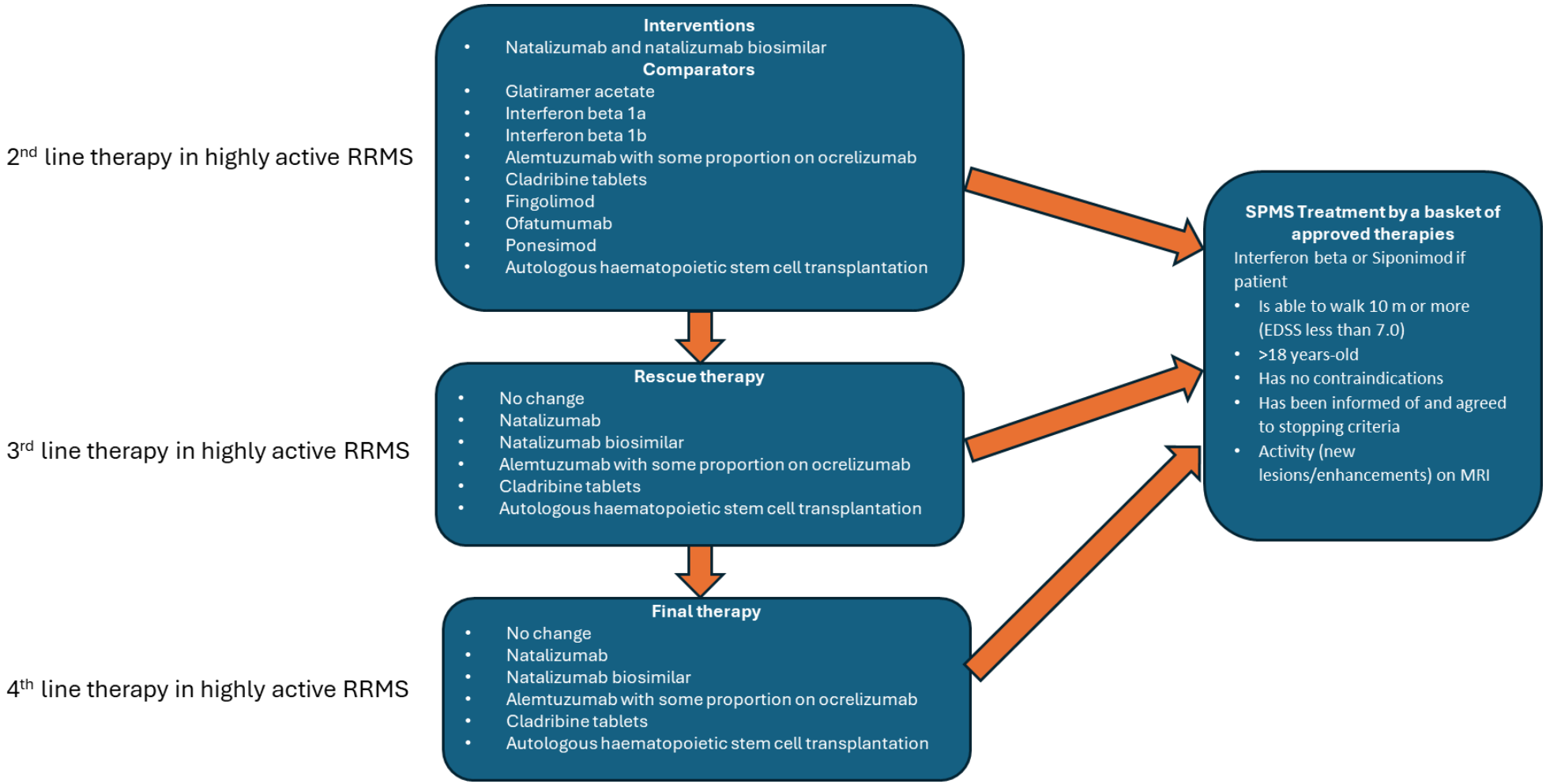


Figure 24 Treatment sequence in the cost-effectiveness DES model



6.5 Input data

6.5.1 Clinical outcomes and treatment effects

The event rates were a combination of natural history (informed by analyses of MS registry data described below) and treatment effects. Treatment effects came from the NMA described in Section 4.3.6. Events for patients with RRMS (i.e., SPMS status = 0) with treatment effects were EDSS increase (i.e., CDP6), relapse (i.e., ARR), serious adverse events, and discontinuation due to adverse events. No treatment effect was assumed for progression to SPMS, EDSS decrease, or mortality. Events for patients with SPMS (i.e., SPMS status = 1) were assumed not to be affected by the RRMS treatment. The natural history data for SPMS patients represents outcomes on the basket of treatments described in Figure 24, and was again informed by MS registry analyses described below.

Proportion of relapses leading to hospitalisation were from observational studies on the costs and utilities of relapses.[118]

Relapse rates in SPMS were informed by the MS registry analyses and included regression on EDSS severity. Rates were expected to decrease with increasing severity, following EAG recommendations in TA699 and rates reported in TA527.[31, 41] In TA767 For people who progressed to SPMS, people were assumed to transition through health states based on the London Ontario dataset.[42]

Regarding the choice of CDP6 instead of CDP3 to represent EDSS decrease, in TA767 the EAG recommended that CDP6 was a more appropriate measure of disease progression following clinical advice that CDP3 may potentially overestimate progression due to natural fluctuations in the disease.[42] CDP6 was also preferred in other previous appraisals.[39]

Baseline rates of discontinuation due to AEs provided a proxy to waning as in previous appraisals, and were assumed to follow the AFFIRM study for natalizumab and ANTELOPE study for natalizumab biosimilar. For comparators we used the NMA on discontinuation due to AEs (Section 5.1.5.) and applied treatment effects to the baseline rates from AFFIRM.

6.5.2 MS Registry analyses

The following data specification was shared with the MS Registry on 8th August 2024. Analyses are separated into those that are essential and those that are desirable. Published sources will be used in place of those that are desirable but infeasible.

6.5.2.1 Requested analyses

We requested rates of events using exponential survival and continuous-time multistate models fit to interval censored data. Covariates were included in some of these models. Outputs needed were model parameters and their covariance matrices on the natural scale (e.g., log rates for exponential and multistate models). Age and sex were considered as covariates in all models but were removed due to limited data.

The model specification is provided in Table 14.

Unless otherwise specified, analyses were conducted in highly active RRMS, any RRMS, and SPMS. The RRMS populations matched those of the NMA, namely highly active RRMS who have received at least one previous DMT, and any RRMS. As noted in Table 2 there is no consensus definition of highly active RRMS. Previous appraisals for NICE have used different definitions. The MS registry aimed to align as closely as possible with our selected definition: Unchanged or increased clinical or radiological evidence of disease activity despite treatment with at least one DMT.

A covariate effect was included to represent treatment. However we did not use the MS registry to estimate hazard ratios as these come from the NMA based on RCT data. The covariate for treatment is only used to obtain baseline rates specific to natalizumab, to which the NMA hazard ratios were applied. Treatments included are the interventions, noting that that Natalizumab biosimilar (Tyruko) was not included in the registry, and the comparators:

- Natalizumab (Tysabri), delivered subcutaneously or intravenously,
- Glatiramer acetate
- Interferon beta 1a
- Interferon beta 1b
- Alemtuzumab
- Cladribine tablets
- Fingolimod
- Ocrelizumab
- Ofatumumab
- Ponesimod

We requested sample sizes and total exposure times to be reported for all analyses in Table 14 and Table 15.

We furthermore requested the EDSS distribution at baseline so as to inform the starting point for our model.

Table 14 Essential requested analyses in RRMS and Highly Active RRMS.*

Event	Effect estimate	Model	Covariates
EDSS increase (i.e., confirmed disability progression)	Rate	Exponential	Treatment, current EDSS
EDSS decrease	Rate	Exponential	Current EDSS
EDSS increase or decrease	Rates	Multistate model with state for each EDSS category (0, 1, …, 9)	Treatment on EDSS increase only
Relapse	Rate	Exponential	Treatment, current EDSS
Progression to SPMS	Rate	Exponential	Current EDSS

*Rates are required separately in two populations: highly active RRMS who have received at least one previous DMT, any RRMS

Table 15 Essential requested analyses in SPMS.

Event	Effect estimate	Model	Covariates
EDSS increase (i.e., confirmed disability progression)	Rate	Exponential	Current EDSS
EDSS increase or decrease	Rates	Multistate model with state for each EDSS category (0, 1, …, 9)	
Relapse	Rate	Exponential	Current EDSS

6.5.3 Utilities

Utilities associated with model attributes (EDSS and SPMS status) were derived from previous appraisals and the SLR on cost-effectiveness evidence (Section 6.1). Disutilities for events (i.e., relapse, adverse events) were also derived from these sources.

The base case utilities are from the UK MS Survey 2005, a cross-sectional study of MS patients (n=2048) with self-reported EQ-5D quality of life and resource use via a postal questionnaire.[128] The authors report the questionnaire was adapted from a descriptive cost of illness study conducted in the UK in 1999 by Kobelt et al[146] the design of which closely follows a cross-sectional study in Sweden by Henriksson et al.[147]

Unlike the studies by Kobelt et al or Henriksson et al, the UK MS Survey patients were self-reporting and had not been assessed in clinic. Disease severity was self-assessed on the Adapted Patient Determined Disease Steps (APDDS) scale but reported by Expanded Disability Scale (EDSS) strata, these scales are used interchangeably by authors although they do not cite evidence in support of this assumption.[148] The distribution of patient characteristics were reported grouped by APDSS 0-3 (21%) APDSS 4-6.5 (60%) and APDSS 7-9.5 (19%).

Multivariate linear regression analysis was used to fit an ANOVA model, and authors reported mean (95% CI) utility stratified by APDSS, relapse, SPMS, PPMS, education (college, university, postgraduate), sex and years since diagnosis. The presented model has moderate explanatory power (R^2=0.478), alternative models were not available. The uncertainty in the estimates for the 11 stratified severity states is such that confidence intervals overlap with each other.

The UK MS Survey 2005 was the source of utility values in TA767, TA699, TA533, TA312, TA254, and TA127. A variation of these utility values were reproduced in TA127 with slightly higher mean estimates by excluding the education variables. Furthermore, disutility of relapse was stratified by severity using data from the AFFIRM trial. Uncertainty was not reported for this analysis, limiting its applicability for our fully probabilistic model.

Trial utilities stratified by severity were used in TA533 by pooling both treatment and placebo arms of OPERA I & II (EDSS 0-5) and combined with Orme et al. (EDSS 6-9). They were used in TA616 by pooling both treatment and placebo arms of CLARITY & CLARITY-EXT (EDSS 0-5) and combined with Hawton et al (EDSS6-8) and Orme et al (EDSS 9) as shown in Table 17. Trial utilities were redacted from TA696 (ASCLEPIOS), TA254 (TRAMSFORMS & FREEDOMS).

A systematic review of utilities in MS identified 16 studies reporting utilities associated with health states in MS as measured by EDSS, 3 of these were UK studies.[149] The manufacturer in TA624 and the ERG in TA767 ran scenarios using the utilities reported in a study by Thompson et al. That data was from the study by Kolbet et al and utility values are broadly similar to Orme. Uncertainty was again not reported for this analysis, limiting its applicability for our fully probabilistic model.

The committee in TA254 preferred utility data from Orme was combined with utility data from key trials. The TA533 committee thought utilities for the rapidly evolving severe subgroup were over estimated.

Table 16 Health state and relapse utilities used in economic model as calculated from the UK MS Survey 2005

	RRMS		**SPMS**	
	Mean	**sd**	**Mean**	**sd**
EDSS0	0.870	0.045	0.825	0.061
EDSS1	0.799	0.093	0.754	0.109
EDSS2	0.705	0.093	0.660	0.108
EDSS3	0.574	0.097	0.529	0.113
EDSS4	0.610	0.093	0.565	0.108
EDSS5	0.518	0.092	0.473	0.108
EDSS6	0.458	0.092	0.413	0.108
EDSS7	0.297	0.094	0.252	0.110
EDSS8	-0.049	0.095	-0.094	0.111
EDSS9	-0.195	0.119	-0.240	0.135
	Mean		**sd**	
Relapse	-0.071		0.016	
Years since diagnosis	0.002		0.001	

Table 17 Health State utility values stratified by severity for RRMS patients. UK MS Survey 2005 model formula and pooled estimates from key trials.

	UK MS Survey 2005			**OPERA**		**CLARITY**	
	Mean	**LCI**	**UCI**	**Mean**	**SE**	**Mean**	**SE**
EDSS0	0.87	0.782	0.958	0.8809	0.0154	0.906	0.026
EDSS1	-0.071	-0.165	0.023	0.8438	0.0072	0.845	0.046
EDSS2	-0.165	-0.259	-0.072	0.7699	0.0061	0.804	0.012

EDSS3	-0.296	-0.398	-0.195	0.7048	0.0069	0.701	0.701
EDSS4	-0.26	-0.354	-0.167	0.6438	0.0088	0.655	0.013
EDSS5	-0.352	-0.444	-0.26	0.6003	0.013	0.565	0.026
EDSS6	-0.412	-0.505	-0.319	0.4909	0.0205	0.573	0.225
EDSS6.5	-0.408	-0.502	-0.314	-	-	0.573	0.225
EDSS7	-0.573	-0.67	-0.477	0.4387	0.0989	0.573	0.225
EDSS8	-0.919	-1.017	-0.82	-	-	0.573	0.225
EDSS9	-1.065	-1.21	-0.919	-	-	0.573	0.225
Recent relapse‡	-0.071	-0.096	-0.046	-0.1006	0.0201	-	-
SPMS	-0.045	-0.076	-0.014	-	-	-	-
Years since diagnosis	0.002	0.001	0.003	-	-	-	-

‡binary variable indicating presence or absence of relapse in the past 3 months.

Carer disutilities for our base case used data from a commonly cited study. This online survey of 200 caregivers by Acaster et al, matched care givers (n=200) with controls from the general population asked (n=400). Respondents self-reported EQ-5D, SF-36 and HADS, MS Disease severity was stratified for using the self-reported PDSS. Authors report significant differences between cases and controls as measured on the SF-36 scale and HADS but the results for EQ-5D uncertain. The manufacturer of Natalizumab utilized caregiver disutilities for patients suffering from Alzheimer's disease in their 2008 submission for TA127.[150]

Table 18 Carer disutilities

	TA127		Acaster et al	
	Mean	SE	Mean	SE
EDSS0	0.000	-	-0.002	0.053
EDSS1	-0.001	-	-0.002	0.053
EDSS2	-0.003	-	-0.045	0.057
EDSS3	-0.009	-	-0.045	0.057
EDSS4	-0.009	-	-0.142	0.062
EDSS5	-0.020	-	-0.16	0.055
EDSS6	-0.027	-	-0.173	0.054
EDSS7	-0.053	-	-0.03	0.038
EDSS8	-0.107	-	-0.095	0.075
EDSS9	-0.140	-	-‡	-

‡ we assumed these to be the same as EDSS8

Serious Adverse Events utility decrements are assumed to be a single Natalizumab specific utility decrement that was calculated as a weighted average of those reported in the AFFIRM trial.[77] The proportion of patients experiencing PML was provided by Biogen[151] using data from the 15 year final Analysis of the TOP study for the global population (n=6321) treated with Natalizumab.[152] The annual utility decrements associated with Serious AEs for Natalizumab have been reported in previous RRMS appraisals as outlined in Table 19.

Table 19 Serious Adverse Events utility decrements assumed for treatments in the model based on the AFFIRM trial

Serious Adverse Events	Utility decrement (annual)	Duration (days)	Utility decrement (per event)	source
Urinary tract infection	-0.10	5	-0.0014	TA767, TA699
Depression	-0.56	365.25	-0.5600	TA699
Anaphylactic reaction	-1.00	7	-0.0192	TA312
Hypersensitivity reaction	-1.00	7	-0.0192	TA616
Breast cancer	-0.1160	365.25	-0.1160	TA616
Gastritis	-0.07	24.5	-0.0047	TA616
PML	-0.30	365.25	-0.3000	TA767, TA699

6.5.4 Costs and resource use

Drug costs were derived from previous appraisals, the SLR on economic evidence described in Section 6.1, and PAS prices provided by NICE. Event costs were derived from previous appraisals and the SLR.

The categories of costs utilized in the economic model include: drug acquisition, drug administration, drug monitoring and serious adverse events costs obtained from the BNF and manufacturer submissions. Health state and relapse costs were obtained from analyses of observational studies widely used in previous submissions. These are assumed to be from a NHS and PSS perspective, unless otherwise stated. Where necessary, costs were inflated to the financial year 2023/2024.

The annual drug acquisition costs are in line with the costs of Natalizumab, Natalizumab bio similar, Ofatumumab and Ocrelizumab reported in the Sandoz submission. The number of annual doses for Natalizumab are in line with those reported in the Biogen submission. The annual number of units prescribed and annual costs were reported in MS single and multiple technology appraisals. We cross referenced list prices with the BNF and the annual units prescribed with our clinical advisors. Annual drug acquisition costs and proportions of patients treated beyond year two are detailed in Table 20. List drug prices for some generics are detailed in Table 26.

Table 20 Annual Treatment acquisition (list prices) quantities, costs and proportion of patients retreated.

Treatment	Year 1		Year 2 onwards		Patients treated (proportion)		
	Units (n)	Cost (£)	Units (n)	Cost (£)	Year 3	Year 4	Year 5+
Ponesimod 20 mg	1 daily	£14,010	1 daily	£14,010	0.75	0.75	0.75
Ofatumumab 50 mg	15	£22,388	15	£17,910	0.95	0.95	0.95
Alemtuzumab 12 mg	5	£35,225	3	£21,135	0.4	0	0
Cladribine Tablets	12-14	£26,373	12-14	£26,373	0.25	0.25	0
Ocrelizumab300 mg	4	£19,160	4	£19,160	0.95	0.95	0.95
Fingolimod500 µg	1 daily	£19,169	daily	£19,169	0.75	0.75	0.75

Treatment	Year 1		Year 2 onwards		Patients treated (proportion)		
	Units (n)	Cost (£)	Units (n)	Cost (£)	Year 3	Year 4	Year 5+
Natalizumab-IV300 mg	13	£14,690	13	£14,690	0.8	0.8	0.8
Natalizumab-SC 300 mg	13	£14,690	13	£14,690	0.8	0.8	0.8
Natalizumab-IV-biosimilar 300 mg	13	£13,221	13	£13,221	0.8	0.8	0.8
Natalizumab-SC-biosimilar 300 mg	13	£13,221	13	£13,221	0.8	0.8	0.8
Peginterferon -β-1a SC 125µg	1 bi-weekly	£8,502	1 bi-weekly	£8,502	0.5	0.5	0.5
Interferon-beta-1a SC 44µg	3 weekly	£10,311	3 weekly	£10,311	0.5	0.5	0.5
Interferon-beta-1a SC 22µg	3 weekly	£7,976	3 weekly	£7,976	0.5	0.5	0.5
Interferon-beta-1a IM 30µg	1 weekly	£8,502	1 weekly	£8,502	0.5	0.5	0.5
Interferon-beta-1b SC 250µg	1 every other day	£7,239	1 every other day	£7,239	0.5	0.5	0.5
Glatiramer acetate SC 20 mg	1 daily	£6,681	1 daily	£6,681	0.5	0.5	0.5
Glatiramer acetate SC 40 mg	1 daily	£6,681	1 daily	£6,681	0.5	0.5	0.5
Patients progressing on to SPMS assumed to be treated with an annual cost for the remaining duration.							
Siponimod	£ 7,239				1		
Peginterferon -β-1a SC 125µg	£8,502				1		

Administration Costs

In previous technology appraisals treatment administration visits were classed as neurology outpatient visit by the manufacturers of Natalizumab-IV,[34] and Fingolimod.[40] Classed as day case (admitted patient care) by the manufacturers of Alemtuzumab,[39] Ocrelizumab,[33] further includes comparators Natalizumab-IV and Fingolimod in manufacturers' submissions.[33, 38-41]

Our clinical advisors agreed that all treatment administration visits are day cases. The HRG grouper code AA30# used to cost day cases,[33, 34, 39] arises out of group of procedures/interventions/diagnoses (IC-10 codes). The exact AA30# is dependent the on the complication and comorbidity (CC) diagnosis for each individual admitted patient.[153] We have assumed that treatment administration visits for Natalizumab-IV, Natalizumab-SC Alemtuzumab and Ocrelizumab require day cases with frequency of visits determined by number of doses.

The manufacturers anticipate cost savings associated with the administration and monitoring of Natalizumab Sub Cutaneous (SC) in comparison to the intravenous (IV)

deliver. However, our clinical advisors explained that in practice patients do not see differences between SC and IV in intensity of resource use. Beta interferons and Ofatumumab are self-administered injections requiring nurses' time to train patients. Tablets; Ponesimod, Cladribine do not require administration day cases with exception of Fingolimod. The detailed administration costs are outline in Table 21

Treatment monitoring visits are required for all treatments which we have assumed to be nurse led outpatient visits. Furthermore, the clinical Advisors pointed out annual MRI monitoring should be undertaken for all treatments and are increasingly routine for Natalizumab and B cell therapies. Monitoring Costs were not included in either of the Sandoz or Biogen submissions, so we have relied on previously published estimates supplemented by clinical advice and updated unit costs. The detailed monitoring costs are in Table 22.

Patients progressing on to SPMS are treated with Peginterferon beta 1a or Siponimod. The annual treatment administration and monitoring cost of £733 was reported in TA656.[30]

Table 21 Annual Treatment Administration Costs

Treatment	Year 1		Year 2 onwards		Source
	Resource Use	Cost	Resource Use	Cost	
Ponesimod	redacted	£139	redacted	£0.00	TA767[42]
Ofatumumab	3 hours of nurse time (Band 7) [34] (£68)	£204	3 hours of nurse time (Band 7) [34]	£204	PSSRU[154] Sandoz [34]
Cladribine Tablets	None	£0.00	None	£0.00	TA616[38]
Alemtuzumab	5 x day case (£626.13)	£3,130.65	3 x day case (£626.13)	£1,878.39	AA30F Medical care of patients with multiple sclerosis, with CC score 0-1. Day case.[155]
Ocrelizumab	3 x day case (£626.13)	£1,878.39	2 x day case (£626.13)	£1,252.26	AA30F Medical care of patients with multiple sclerosis, with CC score 0-1. Day case[155]
Fingolimod	1 x day case	£626.13	None[40]	£0.00	AA30F Medical care of patients with multiple sclerosis,

Treatment	Year 1		Year 2 onwards		Source
	Resource Use	Cost	Resource Use	Cost	
					with CC score 0-1. Day case
Natalizumab – biosimilar-IV Natalizumab-SC	13 x day case (£626.13)	£8,139.69	13 x day case (£626.13)	£8,139.69	AA30F Medical care of patients with multiple sclerosis, with CC score 0-1. Day case[155]
Peginterferon -β-1a SC 25µg Interferon-beta-1a SC 44µg Interferon-beta-1a SC 22µg Interferon-beta-1a IM 30µg Interferon-beta-1b SC 250µg Glatiramer acetate SC 20 mg Glatiramer acetate SC 40 mg	3 hours of nurse time (Band 7)[119]	£204	None[119]	£0.00	PSSRU[154]

Table 22 Annual Treatment Monitoring Costs

Treatment	Year 1		Year 2 onwards		Source
	Resource Use	Cost	Resource Use	Cost	
Ponesimod*	Redacted (£290.20) 1x MRI scan (£334) 0.2 x cardiac day case (£607.29)	£746	Redacted (£228.20) 1x MRI scan (£334) 0.2 x cardiac day case (£607.29)	£684	TA767[42] EB14E Daycase Other Acquired Cardiac Conditions with CC Score 0-2.[38] RD07Z Magnetic Resonance Imaging Scan Requiring Extensive Patient Repositioning[155]
Ofatumumab*	Redacted (£371.11) 1x MRI scan (£334)	£705	Redacted (£306.07) 1x MRI scan (£334)	£641	TA699[41] RD07Z Magnetic Resonance Imaging Scan Requiring Extensive Patient Repositioning[155]
Cladribine Tablets‡	1x neurology (NCL) first visit (£195.74) 2x neurology (NCL) follow up visits (£184.23) 1x MRI scan (£334) 3x Full blood count (£3.37) 1x tuberculin skin test(£60) 1x HBV test(£59)[156] 1x HCV Test(£65)[157]	£1,092	3x neurology (NCL) follow up visits (£184.23) 3x Full blood count (£3.37) 1x HBV test(£59)[156] 1x HCV Test(£65)[157]	£1,021	TA616[38] Consultant Led (CL) / Non-Consultant Led (NCL) 400 Neurology Service WF01B/C Non-Admitted Face-to-Face Attendance, First / Follow-up[155] Pathology services, DAPS04 Clinical biochemistry[155] Multistix 10sg (£41.12 for 100)[158] RD07Z Magnetic Resonance Imaging Scan Requiring Extensive Patient Repositioning[155]

Treatment	Year 1		Year 2 onwards		Source
	Resource Use	Cost	Resource Use	Cost	
Alemtuzumab	1x neurology (NCL) first visit (£195.74) 11x neurology (NCL) follow up visits (£184.23) 12x bio-chemistry test (£1.55) 12x Full blood count (£3.37) 12x Urinalysis (£8.53) 4 x Thyroid function test (£6.48) 1x H. Papilloma V. Test (£85) 1x Tuberculin skin test (£60)[159] 1 x MRI scan (£334)	£2,889	12x neurology (NCL) follow up visits (£184.23) 12x bio-chemistry test (£1.55) 12x Full blood count (£3.37) 12x Urinalysis (£8.53) 4 x Thyroid function test (£6.48) 1x H. Papilloma V. Test (£85) 1 x MRI scan (£334)	£2,817	NCL 400 Neurology Service WF01A/B Non-Admitted Face-to-Face Attendance, First / Follow-up[155] Pathology services, DAPS04 Clinical biochemistry, DAPS05 Haematology, DAPS07 Microbiology[155] Multistix 10sg (£41.12 for 100)[158] RD07Z Magnetic Resonance Imaging Scan Requiring Extensive Patient Repositioning[155] HPV test, Tuberculin skin test.[39, 160]
Ocrelizumab	1x neurology (NCL) first visit (£195.74) 2x neurology (NCL) follow up visits (£184.23) 2x Full blood count (£3.37) 1x liver function (£3.35) 1x varicella zoster virus test (£45)[161] 1 x MRI scan (£334)	£908	3x neurology (NCL) follow up visits (£184.23) 2x Full blood count (£3.37) 1 x MRI scan (£334)	£893	NCL 400 Neurology Service WF01B/C Non-Admitted Face-to-Face Attendance, First / Follow-up[155] Pathology services, DAPS05 Haematology[155] RD07Z Magnetic Resonance Imaging Scan Requiring Extensive Patient Repositioning[155]
Fingolimod	1x neurology (NCL) first visit (£195.74) 3x neurology (NCL) follow up visits (£184.23) 4x Full blood count (£3.37) 4x liver function (£3.35) 2x basic metabolism (£3.35) 0.69x pregnancy test (£3.5) 1x varicella zoster virus test (£45)[161]	£3,719	2x neurology (NCL) follow up visit (£184.23) 2x Full blood count (£3.37) 2x liver function (£3.35) 2x basic metabolism (£3.35) 1 x MRI scan (£334)	£828	NCL 400 Neurology Service WF01A/B Non-Admitted Face-to-Face Attendance, First / Follow-up[155] Pathology services, DAPS04 Clinical biochemistry, DAPS05 Haematology, DAPS09 Other[155] Multistix 10sg (£41.12 for 100)[158] Elective Inpatients DZ22K Unspecified Acute Lower Respiratory Infection with Interventions, with CC Score 9+[8]

Treatment	Year 1		Year 2 onwards		Source
	Resource Use	Cost	Resource Use	Cost	
	0.2x hospitalization (£11,969.84) 1x Ophthalmology (NCL) first visit (£155.06) 1x follow-up Ophthalmology (NCL) visit (£105.46) 1 x MRI scan (£334)				NCL Ophthalmology Service Non-Admitted Face-to-Face Attendance, First / Follow-up[155] RD07Z Magnetic Resonance Imaging Scan Requiring Extensive Patient Repositioning[155]
Natalizumab-IV or SC	1x neurology (NCL) first visit (£195.74) 1 x MRI scan (£334) 1x JC virus PCR (£247) [162] TA127[34] (£89.15)	£777	1x neurology (NCL) follow up visit (£184.23) 1 x MRI scan (£334) 1x JC virus PCR(£247)[162]	£765	NCL 400 Neurology Service WF01A/B Non-Admitted Face-to-Face Attendance, First / Follow-up[155] RD07Z Magnetic Resonance Imaging Scan Requiring Extensive Patient Repositioning[155]
Peginterferon -β-1a SC 125µg Interferon-beta-1a SC 44µg Interferon-beta-1a SC 22µg Interferon-beta-1a IM 30µg Interferon-beta-1b SC 250µg Glatiramer acetate SC 20 mg Glatiramer acetate SC 40 mg	1x neurology (NCL) first visit (£195.74) 4x neurology (NCL) follow up visits (£184.23) 5x liver function test (£3.35) 5x Full blood count (£3.37) 4x renal function test (£3.35) 1x Thyroid function test (£6.48) 1x MRI scan (£334)	£1,320	2x neurology (NCL) follow up visits (£184.23) 2x liver function test (£3.35) 2x renal function test ((£3.35) 1x MRI scan (£334)	£716	CIS Model assumptions[119] Non-Consultant Led (NCL) 400 Neurology Service WF01A/B Non-Admitted Face-to-Face Attendance, First / Follow-up[155] Pathology services, DAPS04 Clinical biochemistry, DAPS05 Haematology[155] Multistix 10sg (£41.12 for 100)[158] RD07Z Magnetic Resonance Imaging Scan Requiring Extensive Patient Repositioning[155]

Health state costs are from the multivariate regression analysis by Tyas et al[130] which combined the per-patient resource use from the 2005 UK MS survey by Orme et al[128] with per unit costs form other data sources to infer per-patient annual costs stratified by severity. These costs have been used extensively in TA767, TA699, TA533, TA312, TA254, T127, MTA (Teva submission). In TA533 it was noted 25% of direct non-medical costs are publicly funded and applicable to the NICE reference case. In TA312 the ERG preferred not to include direct non-medical costs from this analysis. The costs have been inflated to 2022/2023 prices using the NHSCII pay and prices index, details provided in Table 23.[154]

Table 23 Direct medical health state costs by severity, model formula A Tyas et al inflated to 2022/2023 prices

	2022/2023 prices	
	Estimate	**SE**
RRMS‡		
EDSS 0	£355	£2,807
EDSS 1	£121	£1,278
EDSS 2	£303	£1,234
EDSS 3	£1,208	£1,758
EDSS 4	£1,146	£1,257
EDSS 5	£2,017	£1,170
EDSS 6	£3,073	£1,210
EDSS 7	£9,358	£1,414
EDSS 8	£15,297	£1,520
EDSS 9	£21,494	£3,775
SPMS	£398	£1,002

‡ reference category

Serious Adverse Events costs are assumed to be a single Natalizumab specific cost that was calculated as a weighted average of those reported in the AFFIRM trial.[77] The proportion of patients experiencing PML was provided by Biogen[151] using data from the 15 year final Analysis of the TOP study for the global population (n=6321) treated with Natalizumab.[152] Resource use for serious adverse events were based on previous technology appraisals[33, 34, 38] where available and updated to reflect the latest published reference costs.[155] These have been summarised in Table 24.

Table 24 Serious Adverse Events costs assumed for treatments in the model based on the AFFIRM trial

Serious Adverse Events	**Cost**	**Source**
Cholelithiasis	£9,006.35	GA10H Laparoscopic Cholecystectomy, 19 years and over, with CC Score 4+ (average on-elective long stay HRG cost)
Rehabilitation therapy	£618.38	VC12Z Rehabilitation for Other Neurological Disorders (average total HRG cost)
Urinary tract infection	£7,041.01	LA04H Kidney or Urinary Tract Infections, with Interventions, with CC Score 12+ (average non-elective long stay HRG cost)
Depression	£21,521.36	52x WF01B/C Medical Psychotherapy Service Consultant led Non-Admitted Face-to-Face Attendance first visit / follow up visits

Anaphylactic reaction	£3,236.00	DZ22L unspecified acute lower respiratory infection, with interventions, CC 0-8 (average total HRG cost)
Hypersensitivity reaction	£541.61	WH05Z Allergy or Adverse Allergic Reaction (average total HRG Cost)
Breast cancer	£14,212.82	CB0A1 Malignant, Ear, Nose, Mouth, Throat or Neck Disorders, with Interventions, with CC Score 9+ (average non-elective long stay HRG cost)
Gastritis	£706.54	FD05B Abdominal Pain without Interventions (average total HRG cost)
PML	£14,333.02	RD07Z Magnetic Resonance Imaging Scan Requiring Extensive Patient Repositioning (average total HRG cost £334) SA44A single Plasma Exchange (average non-elective long stay HRG cost £934) HC72A Diagnostic Spinal Puncture, 19 years and over (average non-elective inpatient long stay HRG cost £1,645.02) WH07A Hospitalisation Infections or other complications of procedures with Multiple Interventions with CC Score 2+ (average non-elective long stay HRG cost £11,420)

Patients who discontinue treatment are allowed to switch onto one of the higher line treatments. Patients who progress on to SPMS are assumed to be treated with Siponimod or Peginterferon beta 1a for the remainder of their time in the model.

The standardized mortality ratio in base case analysis was reported in a case control study of (N=1822) MS patients follow-up up till death (Jick 2014).[137] An all-cause mortality Hazard ratio 1.68 (95% CI: 1.38-2.05) compared to the general population was estimated using a proportional hazards cox model.

6.5.5 Table of Model Inputs

A summary of all model input parameter, stochastic uncertainty and references are provided below in Table 25.

Table 25 Model inputs, stochastic distributions and sources of data.

Parameters	Estimate	Distribution	Source
Time Horizon	74 years (lifetime)	-	NICE reference case
Discounting	3.5%	-	NICE reference case
Population baseline characteristics			
Initial age	36	-	AFFIRM
Sex (female)	0.7	NA	AFFIRM
Initial EDSS Distribution	Table 26	Dirichlet	MS Registry
Initial SPMS	0%	-	Decision problem is for patients without initial SPMS
Serious Adverse Events	Cholelithiasis (1%) Need for rehabilitation therapy (1%) Urinary tract infection NOS (1%)	NA	AFFIRM TOPS

Parameters	Estimate	Distribution	Source
	Depression (1%) Anaphylactic reaction (1%) Hypersensitivity reaction (1%) Fall (1%) Breast cancer, NOS (1%) Convulsion, NOS (1%) Gastritis, NOS (1%) Cervical dysplasia (1%) Alcohol poisoning (1%) Head injury (1%) Thermal burn (1%) PML (1%)		
Natural History			
Time to EDSS increase HARRMS Time to EDSS increase SPMS Time to EDSS decrease RRMS* Time to EDSS decrease SPMS Time to SP conversion HARRMS Time to relapse HARRMS Time to relapse SPMS	Estimates of parameters of the exponential survival models provided in results Section 6.8.1	Multivariate Normal on the log rate scale	MS Registry analysis
Baseline parameter			
Probability of SAEs	119 events on Natalizumab IV300 arm (n=627)	Beta	AFFIRM
Probability of discontinuation	38 events on Natalizumab IV300 arm (n=627)	Beta	AFFIRM
Proportion of relapses leading to hospitalisations	0.03500583		Hawton 2016
Proportion treated with Siponimod	0.556962025	-	MS Registry
Mortality			
Life tables	General population mortality rates by age and sex	Piecewise exponential	ONS
Standard Mortality Ratio (SMR)	HR 1.68 (95%CI: 2.05-1.38) .	Normal on the Log HR	Jick et al
SMR by EDSS	MR: 1.6 (Mild), 1.84(Moderate), 4.4 (severe).	Normal on the Log HR	Pokorski et al
Treatment Effects			
CDP3	Log Hazard Ratios	Normal	NMA Section 5.1.3
CDP6	Log Hazard Ratios	Normal	NMA Section 5.1.3
ARR	Log Rate Ratios	Normal	NMA Section 5.1.2
SAEs	Log Hazard Ratios	Normal	NMA Section 5.1.5
Discontinuation	Log Hazard Ratios	Normal	NMA Section 5.1.5
Utilities			
Health State	Table 17	lognormal	Orme etal
Carer	Table 18	lognormal	Acaster et al

Parameters	Estimate	Distribution	Source
Relapse	Table 17	Half normal	Orme et al
SAEs	Table 19	Half normal	See table for details
Costs			
Health State	Table 23	Gamma	Tyas et al
Treatment	Table 20	-	BNF
Administration	Table 21	Gamma	See table for details
Monitoring	Table 22	Gamma	See table for details
Relapse	Table 23	Gamma	Hawton et al
SAEs	Table 24	Gamma	See table for details

* The MS Registry found no patients with highly active RRMS who decreased in EDSS so analysis could not be conducted. Model instead uses rate of EDSS decrease from all RRMS.

6.6 Analyses

The model and cost-effectiveness analysis were fully probabilistic with any specific parameter or structural sensitivity analyses also probabilistic.[124, 125]

6.6.1 Validation

A lack of validation and transparency for cost-effectiveness models can be significant barrier to their acceptance by stakeholders and decision makers in Health Technology Assessments (HTA).[163]

The International Society for Outcomes Research (ISPOR) and Society for Medical Decision Making (SMDM) taskforce on modelling have published significant guidelines on the need and methods for validation.[164] The taskforce identified five forms of validation: face validity, verification, cross validation, external validation, and predictive validation. Face validity of the RRMS model has been checked by clinical opinion and verification was checked by Javier Sanchez Alvarez at Evidera. Cross validation is conducted by comparing the estimates of one model with those of others, but this will not be conducted as requires full access to multiple RRMS models. External validation requires the comparison of model estimates with reports from independent external data. Given concerns about estimated occupancy of high EDSS states in TA767 and TA699 and the conversion to SPMS in TA699 and TA127, this is of importance to our RRMS model.[34, 41, 42] We therefore conducted an informal external validation of estimated EDSS against long-term data identified by the searches.

6.6.2 Cost-effectiveness analysis

Lifetime costs and QALYs were estimated. The mean over patient simulations was first calculated, removing individual variation and giving a lifetime cost and QALY estimate for each parameter sample. These were then summarised for each intervention/comparator using their mean and 95% CrI over parameter samples. Incremental costs and QALYs, summarised by means and 95% CrI, were calculated for each comparator compared to natalizumab and natalizumab biosimilar. Base case analyses used 1000 patients and 1000 samples while sensitivities used 100 patients and 100 samples. The number of patients to

simulate and parameters to sample were tested by comparing the mean and 95% CrI, as calculated above, for 100, 250, 500, and 1000 patients and samples.

The primary analysis was a multiple treatment comparison under the net benefit framework. Net benefit and, relative to each intervention, incremental net benefit were calculated at willingness-to-pay of £20,000/QALY and £30,000/QALY. Their mean and 95% CrI were calculated and the treatment with greatest net benefit interpreted as most cost-effective. Cost-effectiveness acceptability curves (CEAC).

A cost-effectiveness plane relative to natalizumab was included but not for natalizumab biosimilar; the high uncertainty and number of treatments give these planes little explanatory value.

A key sensitivity analysis excludes the cost for JCV testing on natalizumab, as a scheme is available whereby the manufacturer pays for this testing (Section 6.4). In this sensitivity, the cost is not excluded for the biosimilar as the scheme does not apply.

While the base case analysis used the cost of primary brands of comparators, a sensitivity analysis used the lowest price generic. This only modifies the price of glatiramer acetate (changing to Brabio manufactured by Viatris UK Healthcare Ltd) and fingolimod (changing to Fingolimod manufactured by Tillomed Laboratories Ltd).

Table 26 generic drug list prices

Drug	Mode	Qty.	Dose	Brand (Manufacturer)	Tariff Price	Indicative Price	delta
Glatiramer acetate	Injection	12	40 mg per 1 ml	Copaxone (Teva UK Ltd)	£513.95	£513.95	
Glatiramer acetate	Injection	12	40 mg per 1 ml	Brabio (Viatris UK Healthcare Ltd)	£513.95	£462.56	10.00%
Fingolimod	Capsule	28	0.5 mg	Gilenya (Novartis Pharmaceuticals UK Ltd)	£1,470.00	£1,470.00	
Fingolimod	Capsule	28	0.25 mg	Fingolimod (Novartis Pharmaceuticals Ltd)		£1,470.00	
Fingolimod	Capsule	28	0.5 mg	Fingolimod (Glenmark Pharmaceuticals Europe Ltd)	£1,470.00	£1,470.00	
Fingolimod	Capsule	28	0.5 mg	Fingolimod (Dr Reddy's Laboratories UK Ltd)	£1,470.00	£1,470.00	
Fingolimod	Capsule	28	0.5 mg	Fingolimod (Amarox UK Ltd)	£1,470.00	NA	
Fingolimod	Capsule	28	0.5 mg	Fingolimod (Sun Pharma UK Ltd)	£1,470.00	£1,470.00	

Drug	Mode	Qty.	Dose	Brand (Manufacturer)	Tariff Price	Indicative Price	delta
Fingolimod	Capsule	28	0.5 mg	Fingolimod (Accord UK Ltd)		£1,469.99	
Fingolimod	Capsule	28	0.5 mg	Fingolimod (Zentiva Pharma UK Ltd)	£1,470.00	£1,396.50	5.00%
Fingolimod	Capsule	28	0.5 mg	Fingolimod (A A H Pharmaceuticals Ltd)		£1,396.50	5.00%
Fingolimod	Capsule	28	0.5 mg	Fingolimod (Teva UK Ltd)	£1,470.00	£1,323.00	10.00%
Fingolimod	Capsule	28	0.5 mg	Fingolimod (Viatris UK Healthcare Ltd)	£1,470.00	£1,250.00	14.97%
Fingolimod	Capsule	28	0.5 mg	Fingolimod (Sandoz Ltd)	£1,470.00	£1,249.50	15.00%
Fingolimod	Capsule	28	0.5 mg	Fingolimod (Tillomed Laboratories Ltd)	£1,470.00	£367.50	75.00%

A summary of the base case and sensitivity cost-effectiveness analyses is provided in Table 27.

Table 27 Description of base case and sensitivity cost-effectiveness analyses

Analysis	Description
Base case	Uses HA RRMS from MS Registry for baseline rates, all RRMS fixed effects from NMA for treatment effects, EDSS starting distribution from MS Registry for HA RRMS. Costs for primary bands are used for comparator drugs.
Scenario 1. Sensitivity using all RRMS and EDSS distribution for all RRMS from MS registry	Changes base case to better match the all RRMS population in the NMA. Uses all RRMS from the MS Registry for both baseline rates and the starting EDSS distribution for all RRMS
Scenario 2. Sensitivity using results of random effects NMAs	Changes base case to use the all RRMS random effects results from the NMA for treatment effects
Scenario 3. Sensitivity including JCV testing	Excludes the one-off cost of £247 associated with JCV testing for the natalizumab IV and SC interventions, but includes it for natalizumab biosimilar IV.
Scenario 4. Sensitivity using lowest price generic	Switches to using lowest price generic for comparators.
Scenario 5. Sensitivity assuming a reduction in Natalizumab-SC administration costs	Reduces administration cost by a factor of 0.5x for Natalizumab-SC to explore the company's assumption of reduced resource use (nurse administration hours per year). Increased capacity for service delivery at home(company funded) or in primary care setting.[34].
Scenario 6. Sensitivity using HA RRMS NMA	HARRMS on ARR only. all RRMS NMA for the other outcomes. Restricted to only the treatments which are included in the HA RRMS NMA for ARR (i.e., alemtuzumab, cladribine, fingolimod, interferon beta 1a, natalizumab IV, ocrelizumab IV)
Scenario 7. Sensitivity using mortality rates stratified by disease severity	Mortality ratios calculated using a Chi square table for MS patients stratified by mild (n=1394), moderate (n=789) and severe (n=165) in analysis by the MS Society of Canada between 1972-1985, by Sadovnik et al 1992 and cited in Pokorski et al 1997.

Analysis	Description
	These ratios are widely used in MS appraisals; TA767, TA699, TA533, TA312, TA254 TA127.

6.6.3 Value of information analysis

Parameter uncertainty was quantified using value of information analysis.[165] The per-person expected value of partial perfect information (EVPPI) was estimated for each parameter or for groups of parameters of interest (e.g., each efficacy and safety treatment effect from the NMA, baseline rates from the MS Registry, utilities, uncertain costs, discontinuation rates, and SAE rates). These constitute a large number of uncertain parameters as, for example, there are 10+ treatments on which we would have treatment effects. We therefore use the Bayesian additive regression trees (BART) method, as implemented in the R package VOI, for EVPPI estimation due to its suitability for EVPPI of many parameters. Alternatives we considered were Generalised additive models (GAM), Gaussian processes (GP), and, if found necessary, Multilevel Monte Carlo (MLMC) simulation were used to estimate EVPPI.[166, 167] This per-person EVPPI was used as the probabilistic decision-theoretic alternative to one-way deterministic sensitivity analysis.

If evidence were available on the incidence of 2nd line highly active RRMS, the population EVPPI could be estimated. However, no evidence on this incidence was identified so only per person EVPPI was included.

6.6.4 Software

The model will be coded in the R programming language.[63, 168, 169] The 'DESCEM package was used for the implementation of DES, 'BCEA' will be used for generating the CEACs and CEAFs, and both 'BCEA' and 'VOI' will be used for value of information analysis.[169]

6.7 Changes from the protocol

The model was changed so that there would be no treatment effects on SPMS progression or mortality. The SLR found no data on SPMS progression. Mortality was not included by the SLR as an outcome of interest, but it was not widely reported. MS may reduce life expectancy, with a recent study estimating life expectancy to be 75.9 years in an MS population compared to 83.4 years in a population matched on sex, age, and region. [9] However, the studies generally included patients in their 30s and 40s so would not be expected to find a great impact on mortality.

The software for model implementation was unchanged but the 'DESCEM' package was used instead of 'simmer' due to its greater focus on health economic modelling.

The targeted search for placebo and standard of care outcomes, and the review of health related quality of life, were not undertaken.

The targeted search on placebo and standard of care outcomes was replaced by an analysis of individual patient data from the UK MS Registry (Section 6.5.2).

The "desirable quested analyses" from the MS Registry were removed as were not conducted. These were to estimated EQ-5D-5L for RRMS and SPMS and to model treatment switching patterns.

We removed the plan to calculate ICERs so as to focus interpretation on the total and incremental net benefits. We kept only one cost-effectiveness plane (for natalizumab-IV) as the uncertainty gave it little explanatory power. We included the CEAC but because of the number of treatments, and that non-natalizumab treatments were coming out with highest probabilities, we decided against including the cost-effectiveness acceptability frontiers.

Only per person EVPPI is calculated as we did not find an estimate of the incidence of HA RRMS that corresponded to our definition.

The ratio of EVPPI to EVPI was not calculated as the number of uncertain parameters in the economic model was 247. We instead calculated the EVPPI of substantial groups of parameters.

Validation was limited to a comparison of EDSS severity over time and not SPMS status, as only evidence on EDSS severity could be found by the literature searches.

6.8 Model Results

6.8.1 Results of the MS Registry analyses

The results of the MS registry analyses exponential survival models are summarised in Table 29 (treatment dependent rates) and Table 31 (treatment independent rates). Samples sizes for the treatment dependent models are in Table 30, while those treatment independent models are in Table 31. These coefficients are on the log scale and the total log rate is calculated by adding the relevant components (i.e., the intercept plus the product of the current EDSS category with EDSS coefficient in all models, plus the coefficient for natalizumab in the treatment dependent models). The covariance matrices for the coefficients are provided in Appendix 7. The economic model was probabilistic so coefficients are sampled from multivariate normal with means in Table 29 and Table 31 and covariance matrices in Appendix 7. The MS Registry found no patients with highly active RRMS who decreased in EDSS so analysis could not be conducted.

Table 28 Number of Highly Active RRMS and RRMS patients by severity state in the MS Registry data set.*

EDSS	0	1	2	3	4	5	6	7	8	9
HARRMS	29	6	56	36	56	26	82	10	0	0
RRMS	50	18	200	188	150	90	214	45	5	0

*301 patients in total in HARRMS and 960 in RRMS.

The results of the multistate model are provided in Appendix 7. Due to the low sample size for the transitions between 9 different EDSS states, the log rates were very extreme between low severity states. For example, the mean rate (i.e., exponent of the log rates) between from EDSS 1 to EDSS 0 was 1041.7, EDSS 0 to EDSS 1 was 434.6 and from EDSS 2 to EDSS 3 was 83.0. It was decided to use only the exponential survival models for EDSS increase and decrease events in the economic model.

Table 29 Log rates and log rate ratios for events with treatment dependence estimated by the MS Registry using exponential survival models*

	Times to EDSS Increase (RRMS Highly Active)	Times to EDSS Increase (All RRMS)	Time to Relapse (RRMS Highly Active)	Time to Relapse (All RMS)
Intercept	-0.93 (-1.94, 0.07)	-2.25 (-2.63, -1.86)	-2.13 (-2.95, -1.3)	-2.63 (-3.08, -2.18)
EDSS	-0.18 (-0.33, -0.03)	-0.17 (-0.25, -0.1)	-0.02 (-0.2, 0.17)	-0.07 (-0.16, 0.01)
Alemtuzumab	-0.34 (-1.49, 0.81)	0.05 (-0.68, 0.78)	0.02 (-2.07, 2.12)	0.18 (-0.58, 0.93)
Cladribine	-3.29 (-5.44, -1.14)	-1.17 (-2.35, 0)	-0.79 (-2.87, 1.29)	0.37 (-1.05, 1.79)
Fingolimod	-2.38 (-3.53, -1.23)	-0.53 (-1.05, -0.01)	-0.21 (-1.1, 0.68)	0.13 (-0.34, 0.6)
Glatiramer Acetate	-1.04 (-2.23, 0.16)	-0.3 (-0.81, 0.2)	-0.52 (-1.49, 0.45)	0.04 (-0.39, 0.48)
Natalizumab	-1.26 (-2.5, -0.02)	0.28 (-0.17, 0.72)	-0.74 (-1.92, 0.43)	0.4 (-0.1, 0.9)
Ocrelizumab	-1.05 (-2.09, 0)	0.37 (-0.06, 0.8)	-0.17 (-1.4, 1.05)	0.29 (-0.36, 0.93)
Ofatumumab	-1.81 (-3.24, -0.38)	-0.02 (-0.72, 0.67)	-1.03 (-3.11, 1.05)	-0.1 (-1.53, 1.32)
Ponesimod	-1.43 (-3.58, 0.72)	-0.51 (-2.49, 1.48)	-0.38 (-2.46, 1.7)	0.23 (-1.76, 2.22)

*The economic model only used the intercept, effect of EDSS, and effect of natalizumab.

Table 30 Samples sizes in MS Registry analyses for treatment dependent events*

Event	N	Alemtuzumab	Cladribine	Fingolimod	Glatiramer acetate	Natalizumab	Ocrelizumab	Ofatumumab	Ponesimod
Time to EDSS Increase (RRMS Highly Active)	224	12	23	65	20	23	43	25	4
Time to EDSS Increase (All RRMS)	1016	41	35	158	158	177	203	69	7
Time to Relapse (RRMS Highly Active)	50	1	1	13	11	7	4	1	1
Time to Relapse (All RRMS)	191	9	2	34	44	28	15	2	1

* The MS Registry found no patients with highly active RRMS who decreased in EDSS so analysis could not be conducted.

Table 31 Log rates and log rate ratios for events with no treatment dependence estimated by the MS Registry using exponential survival models

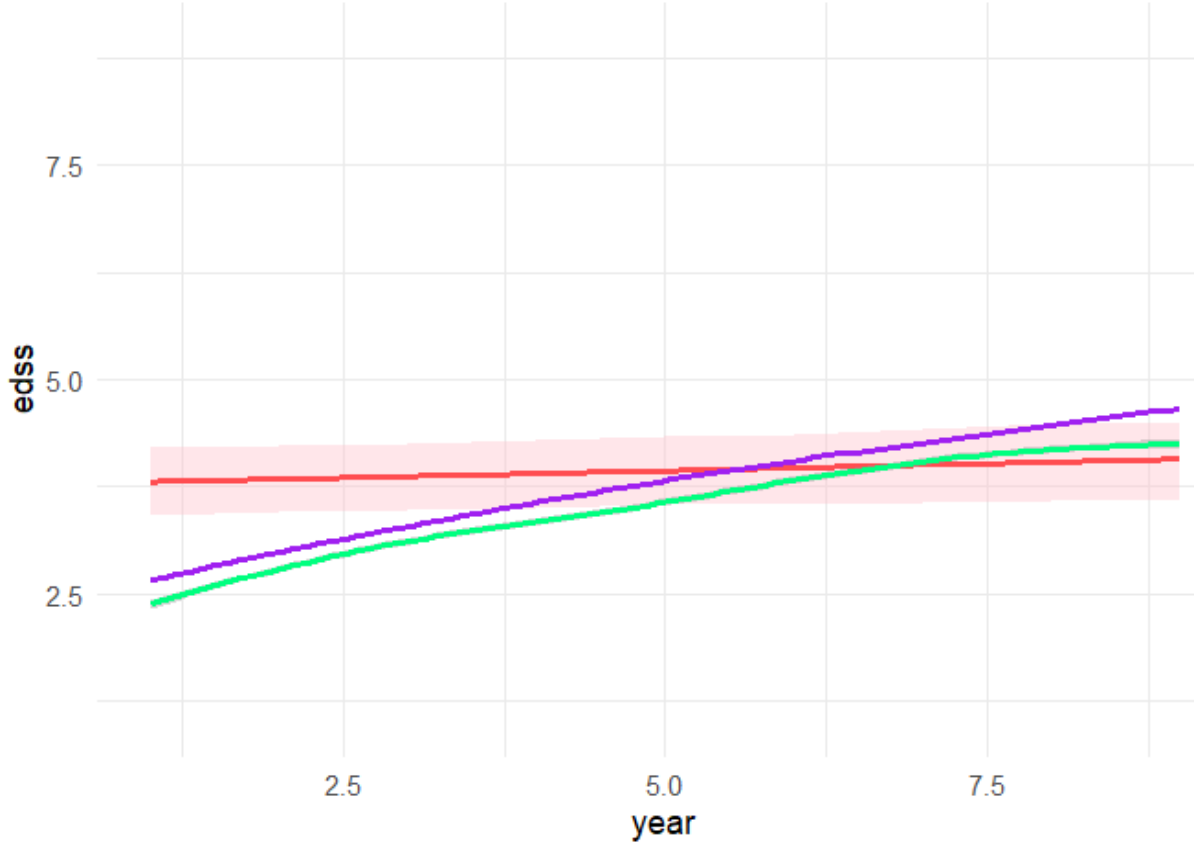
	Time to EDSS Decrease (All RRMS)*	Time to EDSS Increase (SPMS)	Time to Relapse (SPMS)	Time to SPMS Conversion (RRMS Highly Active)	Time to SPMS Conversion (All RRMS)
Sample size	793	181	164	66	222
Rate	-3.51 (-3.94, -3.08)	-1.89 (-3.15, -0.63)	-4.83 (-6.66, -3.01)	-2.58 (-3.89, -1.26)	-2.81 (-3.52, -2.1)
EDSS	0.14 (0.04, 0.23)	-0.2 (-0.42, 0.01)	0.07 (-0.22, 0.36)	0.01 (-0.21, 0.23)	0.04 (-0.08, 0.15)

* The MS Registry found no patients with highly active RRMS who decreased in EDSS so analysis could not be conducted.

6.8.2 Validation

The model code was validated by Javier Sanchez Alvarez at Evidera who found no major issues but suggested some minor improvements to flow and usage of DESCEM.

Figure 25 Validation through comparison of EDSS severity over time from economic model (red line with 95% CrI) and predictions from Palace 2014 (purple and green)



We compare the model's predictions to a continuous-time Markov model fit in to predict EDSS progression in a natural history cohort based on entry demographic and clinical data, but which did not distinguish between RRMS and SPMS, was not specific to highly active RRMS, and only included treatment with beta interferons rather than the latest DMT sequences. The model was fit in a cohort of the UK Risk Sharing Scheme and validated in a closely matched cohort from the British Columbia Canada Data set.[170] The mean (redline) and 95% CrI (shaded area) severity over the first 10 years in our DES model. The purple and green lines are the predicted and observed mean severity over the same time period in the published continuous-time Markov models.[126] The general overlap over this 10 year period is poor and the progression of the DES is less marked. This is likely explained by the comparator model being developed for both RRMS and SPMS and not including the latest DMT sequences.

6.8.3 Base case analysis

The results of the convergence test are in Table 32. This show that the mean and 95% CrI for total costs, QALYs, and net benefits for natalizumab-IV are somewhat stable with only 100 patients and 100 samples. The QALYs are potentially unstable below 500 samples and 250 patients but not to the extent that could affect results. We can therefore use 100 patients and 100 samples for sensitivity analysis as this is sufficient to demonstrate sensitivity or otherwise to the explored assumption.

Table 32 Assessment of convergence of economic model using mean and 95% CrI for natalizumab-IV (publicly available list prices)

		100 samples	250 samples	500 samples	1000 samples
Total costs	**100 patients**	445472.50 (384656.65, 509474.14)	444492.41 (386345.23, 509371.78)	446070.50 (386020.17, 517116.33)	446722.86 (384447.35, 524336.57)
	250 patients	444579.64 (384496.23, 507860.53)	444660.35 (390839.71, 509576.99)	446462.19 (388384.41, 514534.77)	446827.19 (388053.27, 519831.46)
	500 patients	444352.17 (385221.63, 503746.48)	444374.31 (387993.11, 507067.87)	446253.58 (386560.01, 512472.00)	446718.85 (387718.03, 523731.01)
	1000 patients	444033.08 (387382.41, 503238.51)	444304.18 (387987.75, 507098.10)	446291.36 (389490.23, 513545.21)	446764.59 (388187.03, 522503.46)
Total QALYs	**100 patients**	11.17 (6.88, 13.96)	11.14 (7.90, 14.06)	11.23 (7.65, 14.24)	11.24 (7.57, 14.35)
	250 patients	11.22 (7.10, 14.44)	11.17 (7.68, 14.25)	11.24 (7.83, 14.11)	11.24 (7.79, 14.33)
	500 patients	11.19 (7.24, 14.45)	11.16 (7.71, 14.17)	11.24 (7.80, 14.17)	11.24 (7.78, 14.21)
	1000 patients	11.19 (7.37, 14.39)	11.17 (7.77, 14.06)	11.24 (7.80, 14.13)	11.24 (7.82, 14.24)
Net benefit at £20,000/QALY	**100 patients**	-222100.21 (-315910.74, -147473.73)	-221623.97 (-311437.80, -151447.38)	-221445.97 (-321909.96, -142724.31)	-221851.40 (-331455.40, -141065.67)
	250 patients	-220083.86 (-327530.00, -148019.42)	-221256.83 (-313627.18, -155317.50)	-221716.31 (-319519.28, -147883.01)	-222033.01 (-324006.64, -146689.45)
	500 patients	-220558.05 (-322712.11, -146683.00)	-221138.91 (-321733.35, -157801.16)	-221416.46 (-325079.54, -148819.25)	-221925.01 (-325677.31, -148858.02)
	1000 patients	-220193.42 (-316098.78, -148549.24)	-220965.56 (-318089.52, -157068.85)	-221407.43 (-320050.45, -152547.75)	-221930.81 (-325860.27, -150887.39)
Net benefit at £30,000/QALY	**100 patients**	-110414.07 (-245243.77, -17389.21)	-110189.75 (-226669.27, -21420.45)	-109133.71 (-241461.47, -8006.11)	-109415.67 (-245068.55, -7896.10)
	250 patients	-107835.97 (-249433.06, -8308.71)	-109555.07 (-230754.67, -21452.04)	-109343.37 (-233895.66, -10332.30)	-109635.92 (-238812.72, -12210.18)

		100 samples	250 samples	500 samples	1000 samples
	500 patients	-108660.99 (-243280.18, -17087.04)	-109521.20 (-242563.36, -25297.47)	-108997.89 (-246339.94, -16767.23)	-109528.09 (-244229.56, -15209.80)
	1000 patients	-108273.59 (-234743.88, -20799.59)	-109296.25 (-237325.93, -27301.52)	-108965.46 (-240913.49, -20119.42)	-109513.92 (-241330.58, -18726.67)

The results of the base case analysis using the HARRMS population from the MS Registry and base case NMA results (i.e., fixed effects analysis in the All RRMS population) are provided in this section. We used 1000 samples and 1000 patients for this simulation. Uncertainty, as indicated by the 95% CrI is very high but general patterns can be seen.

With the exception of ocrelizumab, all treatments had greater net benefit at £20-30,000/QALY than natalizumab-IV, natalizumab biosimilar-IV and natalizumab-SC. The 95% CrI for incremental net benefits relative to natalizumab-IV excluded zero and the 95% CrI for net benefits for natalizumab biosimilar-IV and natalizumab-SC were not overlapping with those of comparators, indicating confidence that the net benefits of the natalizumabs are lower. Ocrelizumab had lower net benefit than any of the natalizumabs. Natalizumab-IV has lower net benefit at £20-30,000/QALY than natalizumab biosimilar-IV, although the 95% CrI overlap with 0.0 indicating no evidence of a difference in net benefits. Natalizumab-SC has very similar mean net benefit to Natalizumab-IV.

Across treatments, glatiramer Acetate 20mg and 40mg have the greatest net monetary benefits at £20-30,000/QALY, followed by interferon-beta-1a SC 44µg and interferon-beta-1b SC 250µg.

Table 33 Net Benefit and incremental net benefit in for treatments in comparison to Natalizumab IV (Public list prices) for the base case (HARRMS)

Treatment	Net benefit at £20,000/QALY (95% CrI)	Net benefit at £30,000/QALY (95% CrI)	INB at £20,000/QALY (95% CrI)	INB at £30,000/QALY (95% CrI)	CEAC at £20,000/QALY	CEAC at £30,000/QALY
Natalizumab -IV	-221930.81 (-325860.27, -150887.39)	-109513.92 (-241330.58, -18726.67)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0	0
Natalizumab -SC	-221816.85 (-325779.04, -150089.10)	-109261.82 (-242489.08, -12993.23)	113.96 (-19952.71, 20391.27)	252.10 (-22509.33, 23031.01)	0	0
Natalizumab biosimilar-IV	-211500.56 (-316036.43, -141710.58)	-99158.71 (-235407.06, -4747.04)	10430.25 (-9866.37, 33118.11)	10355.21 (-12501.66, 36094.29)	0	0
Fingolimod	-2e+05 (-3e+05, -134564.90)	-94311.01 (-220151.54, 1275.82)	17287.91 (-7082.76, 45155.59)	15202.91 (-12047.99, 45526.85)	0	0

Treatment	Net benefit at £20,000/QALY (95% CrI)	Net benefit at £30,000/QALY (95% CrI)	INB at £20,000/QALY (95% CrI)	INB at £30,000/QALY (95% CrI)	CEAC at £20,000/QALY	CEAC at £30,000/QALY
Alemtuzumab	-152392.62 (-276918.47, -67219.64)	-38961.07 (-194203.82, 71584.52)	69538.19 (-6695.87, 161476.86)	70552.85 (-9314.54, 164282.34)	0.003	0.005
Cladribine	-150332.71 (-275648.38, -56964.47)	-42513.74 (-2e+05, 74956.72)	71598.10 (4838.93, 154730.42)	67000.17 (-1139.26, 150009.19)	0	0
Ponesimod	-165188.69 (-291888.18, -91638.04)	-55654.88 (-218236.52, 44700.22)	56742.12 (14675.92, 1e+05)	53859.04 (5779.06, 99977.03)	0	0
Ofatumumab	-211098.14 (-316552.83, -141119.09)	-98494.07 (-236561.98, -7018.57)	10832.67 (-10896.15, 31986.99)	11019.85 (-16076.43, 35701.92)	0	0
Ocrelizumab	-223985.21 (-332413.48, -152208.74)	-111270.42 (-239271.93, -18105.73)	-2054.40 (-28173.17, 20457.65)	-1756.50 (-32266.54, 24285.25)	0	0
Peginterferon -β-1 SC 125µg	-106013.63 (-219477.93, -29343.97)	6109.89 (-136070.05, 107045.38)	115917.18 (53804.14, 188910.01)	115623.81 (50564.10, 186451.39)	0.264	0.311
Interferon-beta-1a SC 22µg	-119106.47 (-239882.00, -40586.41)	-7852.16 (-158279.13, 94944.57)	1e+05 (44991.63, 170168.40)	1e+05 (41745.72, 169892.42)	0.02	0.035
Interferon-beta-1a SC 44µg	-112006.15 (-242641.36, -28367.59)	-2203.32 (-162378.25, 108832.39)	109924.66 (44792.20, 180986.40)	107310.59 (40296.34, 181737.90)	0.06	0.077
Interferon-beta-1a IM 30µg	-118921.02 (-247888.19, -34500.47)	-10163.40 (-175931.60, 1e+05)	1e+05 (41729.36, 175767.26)	99350.52 (35020.88, 172631.09)	0.01	0.016
Interferon-beta-1b SC 250µg	-112632.59 (-245651.67, -24389.30)	-4104.95 (-172738.91, 112113.78)	109298.22 (42980.66, 186758.07)	105408.97 (33814.12, 184712.12)	0.092	0.083
Glatiramer Acetate 20mg	-105659.02 (-234955.60, -18835.48)	3875.40 (-161256.44, 119588.55)	116271.79 (49230.69, 189757.44)	113389.31 (43692.80, 187217.79)	0.262	0.233
Glatiramer Acetate 40mg	-106021.95 (-233241.35, -20311.08)	3401.66 (-160842.66, 117148.40)	115908.86 (52235.22, 191921.67)	112915.58 (47344.46, 188242.01)	0.289	0.24

The total costs and QALYs for all included treatments, and their incremental comparison with Natalizumab IV, are provided in Table 34. The 95% CrI for both costs and QALYs are wide, suggesting high uncertainty. All treatments, with the exception of ocrelizumab have lower costs than natalizumab-IV with 95% CrI for incremental costs excluding 0.0 and indicating that costs are lower on the comparators. Except for ocrelizumab, and ofatumumab in comparison with natalizumab biosimilar-IV, all 95% CrI for costs on comparators do not overlap with those for natalizumab biosimilar-IV or natalizumab SC, suggesting costs are also higher. The 95% CrI for QALYs were overlapping suggesting no difference, although the mean QALYs were lower on most treatments than on the

natalizumab. The exceptions were alemtuzumab, ofatumumab, and ocrelizumab, which had higher mean QALYs (although ofatumumab was tied with natalizumab-SC).

The natalizumab biosimilar-IV has lower costs but also lower QALYs than natalizumab-IV. However the differences in costs and QALYs are uncertain with 95% CrI overlapping. The 95% CrI for incremental costs and QALYs of natalizumab biosimilar-IV and natalizumab-IV are overlapping with 0.0 suggesting no evidence of a difference in costs or QALYs. Natalizumab-SC has very similar costs and QALYs to natalizumab-IV.

Across treatments, total costs are lower on fingolimod, alemtuzumab, cladribine, and ponesimod than on the natalizumab treatments with 95% CrI that do not overlap. QALYs appear to be lower on fingolimod, cladribine, and ponesimod but uncertainty is higher and the 95% CrI are overlapping.

We see that alemtuzumab has the greatest mean QALYs, followed by ocrelizumab. Ocrelizumab also has the highest costs, followed by natalizumab-SC, which is almost level with natalizumab-IV. The favourable net benefits for glatiramer Acetate 20mg and 40mg, interferon-beta-1a SC 44µg, and interferon-beta-1b SC 250µg, are seen to be driven by their having the lowest costs, despite their low QALYs.

Table 34 Total and incremental costs and QALYs for treatments in comparison to Natalizumab IV (Public list prices) for the base case (HARRMS)

Treatment	Total costs £ (95% CrI)	Total QALYs (95% CrI)	Incremental costs £ (95% CrI)	Incremental QALYs (95% CrI)
Natalizumab-IV	446764.59 (388187.03, 522503.46)	11.24 (7.82, 14.24)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)
Natalizumab-SC	446926.92 (389334.27, 525252.77)	11.26 (7.75, 14.24)	162.33 (-17068.04, 17934.54)	0.014 (-0.42, 0.41)
Natalizumab biosimilar-IV	436184.26 (381421.18, 508599.25)	11.23 (7.77, 14.26)	-10580.33 (-30737.92, 6946.76)	-0.0075 (-0.41, 0.43)
Fingolimod	425306.68 (377192.22, 487796.53)	11.03 (7.61, 14.09)	-21457.91 (-46859.83, -1646.99)	-0.21 (-0.68, 0.26)
Alemtuzumab	379255.72 (330988.23, 443641.14)	11.34 (7.71, 14.36)	-67508.87 (-155132.70, 1749.04)	0.10 (-0.41, 0.63)
Cladribine	365970.64 (316216.65, 431692.60)	10.78 (7.11, 13.95)	-80793.95 (-167683.94, -15278.73)	-0.46 (-1.10, 0.088)
Ponesimod	384256.30 (342207.84, 453538.80)	10.95 (7.26, 14.05)	-62508.29 (-105287.10, -28331.84)	-0.29 (-1.06, 0.25)
Ofatumumab	436306.27 (381061.14, 5e+05)	11.26 (7.95, 14.14)	-10458.33 (-27281.97, 3504.06)	0.019 (-0.53, 0.53)

Treatment	Total costs £ (95% CrI)	Total QALYs (95% CrI)	Incremental costs £ (95% CrI)	Incremental QALYs (95% CrI)
Ocrelizumab	449414.79 (386810.14, 525045.39)	11.27 (7.75, 14.11)	2650.19 (-12692.16, 20848.86)	0.03 (-0.54, 0.62)
Peginterferon -β-1 SC 125µg	330260.67 (290256.33, 388923.34)	11.21 (7.80, 14.17)	-116503.92 (-184620.72, -58258.85)	-0.029 (-0.60, 0.56)
Interferon-beta-1a SC 22µg	341615.11 (3e+05, 4e+05)	11.13 (7.71, 14.10)	-105149.49 (-172331.26, -50539.06)	-0.12 (-0.73, 0.42)
Interferon-beta-1a SC 44µg	331611.79 (289797.35, 4e+05)	10.98 (7.49, 14.03)	-115152.80 (-185982.35, -57567.98)	-0.26 (-0.91, 0.26)
Interferon-beta-1a IM 30µg	336436.28 (294318.50, 405345.27)	10.88 (7.13, 13.97)	-110328.31 (-181158.37, -51670.35)	-0.37 (-1.12, 0.20)
Interferon-beta-1b SC 250µg	329687.88 (285495.32, 4e+05)	10.85 (7.18, 14.03)	-117076.71 (-190840.46, -56263.43)	-0.39 (-1.15, 0.20)
Glatiramer Acetate 20mg	324727.86 (280404.33, 389771.40)	10.95 (7.19, 14.10)	-122036.73 (-195613.46, -58804.24)	-0.29 (-0.93, 0.23)
Glatiramer Acetate 40mg	324869.17 (281520.26, 390156.24)	10.94 (7.26, 14.02)	-121895.43 (-196665.10, -61498.05)	-0.30 (-0.98, 0.21)

The cost-effectiveness plane and CEAC are presented in Figure 26 and Figure 27, respectively. The cost-effectiveness plane graphically illustrates the high uncertainty in incremental costs and effects of Table 34. It also makes it clear that natalizumab-IV is very unlikely to be cost-effective at a £30,000/QALY willingness-to-pay threshold compared to any of the treatments. The CEAC confirms the finding that glatiramer Acetate 20mg, glatiramer acetate 40mg, and interferon-beta-1b SC 250µg are most likely to be cost-effective in the £20-30,000/QALY range. These CEAC values at £20,000/QALY and £30,000/QALY are also reported in Table 33. However, the probability that any one of them has the greatest net benefit is below 25%, indicating high uncertainty as to which is most cost-effective. The natalizumabs have close to 0% chance of having highest net benefit (CEAC) at £20,000/QALY and £30,000/QALY.

Figure 26 Cost-Effectiveness Plane for treatments in comparison to Natalizumab IV, WTP £30,000/QALY (Public list prices) for the base case (HARRMS)

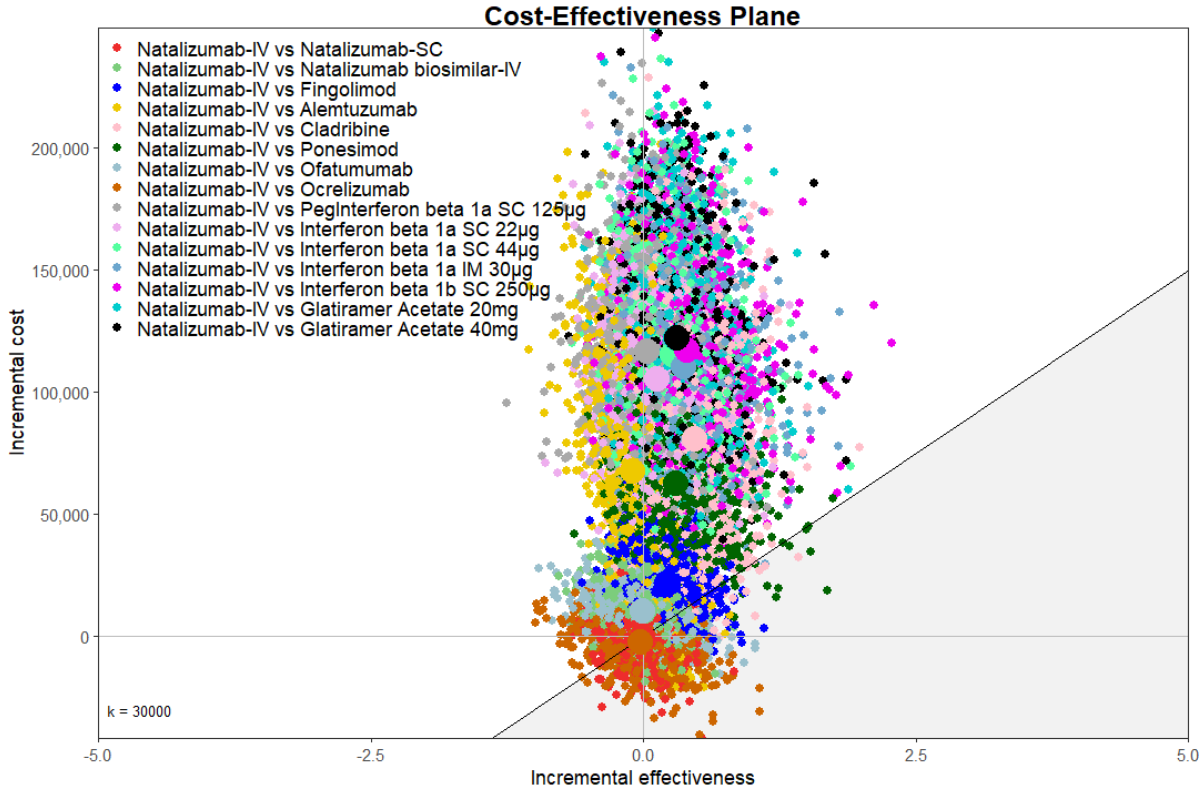
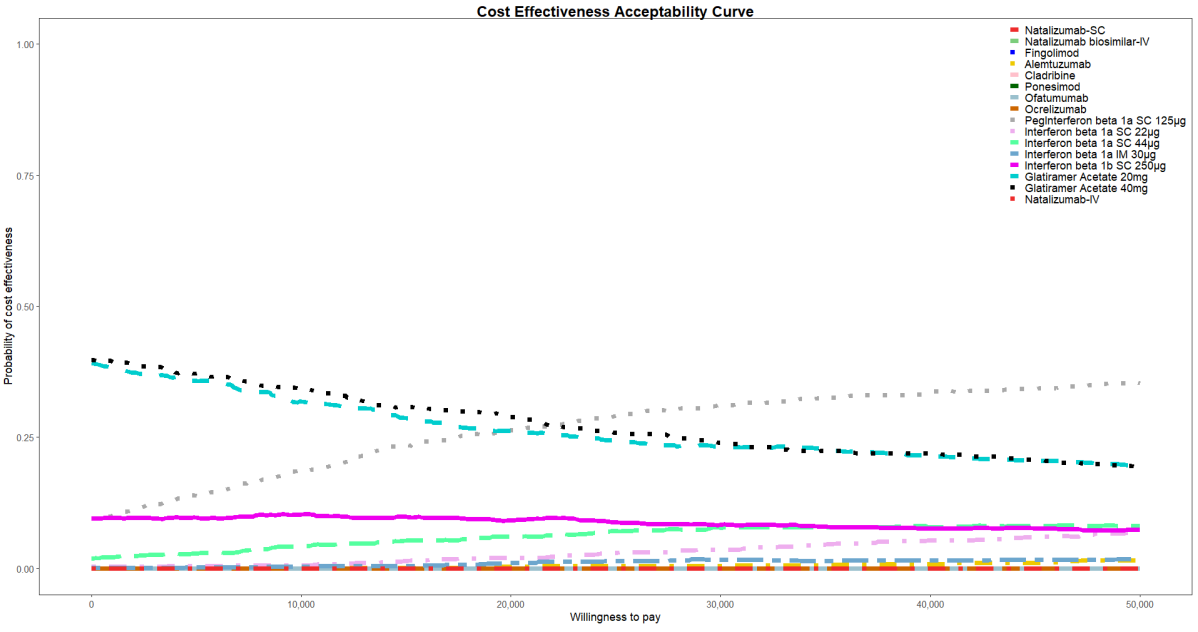


Figure 27 Cost Effectiveness Acceptability Curve for treatments in comparison to Natalizumab IV, WTP £30,000 (Public list prices)



6.8.4 Sensitivity analyses

The incremental net benefits from the sensitivity analyses at £20,000/QALY are presented in Table 35 and at £30,000/QALY in Table 36. We used 100 samples and 100 patients for these simulations.

These sensitivities again find that natalizumab-IV has lower net benefit at £20-30,000/QALY than natalizumab biosimilar-IV with very little impact on the mean results.

Glatiramer Acetate 20mg and 40mg, interferon-beta-1b SC 250µg, and interferon-beta-1a SC 44µg all have the greatest net benefits under all sensitivities except that using the HA RRMS fixed effects NMA which did not include these treatments. In this sensitivity Peginterferon-β-1 SC 125µg was the most cost-effective treatment.

Table 35 Incremental net benefits relative to natalizumab-IV at £20,000/QALY for the base case and sensitivity analyses (publicly available list prices)

Treatment	Base case	Scenario 1 (All RRMS MS Registry population)	Scenario 2 (base-case w/ random effects NMA)	Scenario 3 (base-case & assuming JCV testing provided free of charge by manufacturers)	Scenario 4 (using lowest price generics for comparators)	Scenario 5 (base case & assuming a reduction in Natalizumab-SC administration costs)	Scenario 6 (base-case w/ HA RRMS fixed effects NMA)	Scenario 7 (stratifying mortality by EDSS severity)
Natalizumab-SC	113.96 (-19952.71, 20391.27)	4895.89 (-39205.98, 49241.71)	1328.30 (-43407.17, 50042.28)	301.92 (-54443.94, 42594.90)	290.30 (-54703.54, 43027.00)	29595.30 (-27040.98, 78970.81)	-1446.96 (-46684.75, 44816.42)	-1185.43 (-59638.17, 51227.82)
Natalizumab biosimilar-IV	10430.25 (-9866.37, 33118.11)	8419.56 (-42300.57, 61986.08)	10165.51 (-25734.68, 62974.00)	7491.13 (-36096.45, 47657.00)	9244.85 (-34755.73, 49310.20)	9382.04 (-34051.04, 50103.86)	NA	8876.76 (-40353.52, 59885.62)
Fingolimod	17287.91 (-7082.76, 45155.59)	10953.73 (-39440.55, 70030.22)	21094.72 (-28741.59, 76532.03)	14397.26 (-33316.28, 70273.81)	114805.14 (26396.68, 202734.77)	16193.94 (-32763.50, 72469.58)	13749.84 (-47882.38, 66118.75)	17016.27 (-29082.15, 64385.05)
Alemtuzumab	69538.19 (-6695.87, 161476.86)	66281.33 (-7385.52, 148491.50)	66645.95 (-36459.02, 185053.43)	70322.96 (-30347.06, 164138.11)	72093.83 (-29439.92, 166806.60)	72098.62 (-29906.08, 165748.81)	64895.74 (-22650.54, 154990.93)	68363.73 (-36852.72, 154550.75)
Cladribine	71598.10 (4838.93, 154730.42)	54218.68 (1825.62, 109582.27)	69437.69 (-17083.99, 160907.84)	68491.77 (-19872.07, 144966.82)	70262.12 (-18885.64, 147451.02)	70306.24 (-18928.13, 146517.30)	67090.14 (-21620.01, 141883.97)	67947.25 (-14882.37, 146343.98)
Ponesimod	56742.12 (14675.92, 100225.55)	49249.72 (6668.01, 106365.21)	55898.88 (-11376.28, 116166.09)	55682.28 (-5229.59, 118928.12)	57449.86 (-3895.69, 121424.61)	57409.60 (-3771.59, 120518.98)	NA	53997.48 (-14671.74, 96935.81)
Ofatumumab	10832.67 (-10896.15, 31986.99)	11382.52 (-33304.37, 61448.23)	9759.87 (-65303.87, 61190.89)	5482.83 (-40455.40, 52093.46)	7245.96 (-38857.24, 54118.01)	7387.25 (-37914.90, 55350.90)	NA	6605.59 (-49142.68, 51597.14)

Treatment	Base case	Scenario 1 (All RRMS MS Registry population)	Scenario 2 (base-case w/ random effects NMA)	Scenario 3 (base-case & assuming JCV testing provided free of charge by manufacturers)	Scenario 4 (using lowest price generics for comparators)	Scenario 5 (base case & assuming a reduction in Natalizumab-SC administration costs)	Scenario 6 (base-case w/ HA RRMS fixed effects NMA)	Scenario 7 (stratifying mortality by EDSS severity)
Ocrelizumab	-2054.40 (-28173.17, 20457.65)	4164.11 (-45204.89, 58868.11)	1708.60 (-46988.96, 50625.63)	173.86 (-42704.81, 43363.17)	1947.05 (-41307.01, 45096.64)	1846.71 (-42278.11, 44735.24)	-2009.33 (-47146.53, 54952.96)	-1571.86 (-45018.49, 53735.56)
Peginterfero-beta-1 SC 125µg	115917.18 (53804.14, 188910.01)	106726.98 (56754.96, 156352.89)	114103.51 (39198.21, 191816.07)	112535.34 (37503.05, 183902.04)	114297.43 (38606.47, 186117.59)	114333.26 (38163.78, 186039.19)	111205.44 (49307.15, 188195.60)	113526.59 (32332.44, 188505.75)
Interferon-beta-1a SC 22µg	102824.34 (44991.63, 170168.40)	95157.12 (35795.90, 161703.99)	98413.09 (33653.88, 166618.89)	101087.49 (26832.76, 168413.44)	102862.79 (27804.59, 170745.92)	102762.18 (28027.37, 169978.27)	98865.00 (23759.36, 163764.60)	102264.10 (26814.28, 158608.11)
Interferon-beta-1a SC 44µg	109924.66 (44792.20, 180986.40)	99150.87 (39185.50, 164114.74)	107898.51 (15575.28, 181921.57)	106575.04 (20511.69, 192287.76)	108332.44 (21444.88, 194909.59)	108480.56 (20722.21, 193998.53)	109892.07 (39143.65, 198658.03)	103556.87 (20850.92, 177562.31)
Interferon-beta-1a IM 30µg	103009.79 (41729.36, 175767.26)	92515.34 (33963.26, 152783.19)	96923.71 (10162.06, 168693.98)	99145.04 (23411.19, 187905.73)	100903.52 (24834.30, 190502.16)	100989.74 (23544.30, 189843.94)	103990.45 (15486.56, 172648.50)	102256.18 (21344.63, 179800.06)
Interferon-beta-1b SC 250µg	109298.22 (42980.66, 186758.07)	98342.19 (43882.25, 154030.78)	113495.87 (34404.90, 192017.80)	106228.93 (29844.59, 174330.93)	108000.87 (30736.55, 177233.90)	108086.04 (30784.82, 178134.93)	NA	105714.15 (26192.83, 165685.15)
Glatiramer Acetate 20mg	116271.79 (49230.69, 189757.44)	104948.30 (54206.04, 159494.22)	115594.65 (31042.04, 202626.77)	114316.36 (22861.02, 186364.60)	119723.46 (26230.62, 194240.47)	116067.04 (24066.83, 189715.74)	NA	115586.80 (33579.76, 192430.82)
Glatiramer Acetate 40mg	115908.86 (52235.22, 191921.67)	106969.47 (40479.92, 166503.76)	117613.64 (48215.02, 199974.13)	114998.37 (41676.74, 199230.85)	120378.23 (44910.10, 207373.20)	116760.09 (42665.33, 202742.31)	NA	113011.73 (28420.26, 185119.68)

Table 36 Incremental net benefits relative to natalizumab-IV at £30,000/QALY for the base case and sensitivity analyses (publicly available list prices)

Treatment	Base case	Scenario 1 (All RRMS MS Registry population)	Scenario 2 (base-case w/ random effects NMA)	Scenario 3 (base-case & assuming JCV testing provided free of charge by manufacturers)	Scenario 4 (using lowest price generics for comparators)	Scenario 5 (base case & assuming a reduction in Natalizumab-SC administration costs)	Scenario 6 (base-case w/ HA RRMS fixed effects NMA)	Scenario 7
Natalizumab-SC	252.10 (-22509.33, 23031.01)	5548.49 (-48143.47, 57612.35)	1431.53 (-54958.94, 66479.75)	555.47 (-68423.97, 52051.14)	543.85 (-68683.56, 52260.97)	29848.85 (-40966.08, 88221.33)	-1327.19 (-60521.37, 57139.10)	-1063.34 (-70158.88, 64174.15)
Natalizumab biosimilar-IV	10355.21 (-12501.66, 36094.29)	7535.00 (-54971.50, 68887.44)	9557.75 (-31713.85, 71892.32)	7155.86 (-45802.04, 61464.69)	8909.58 (-44461.32, 63133.78)	9046.77 (-44081.77, 63525.38)	NA	8724.10 (-51873.52, 71749.68)
Fingolimod	15202.91 (-12047.99, 45526.85)	7703.02 (-53853.19, 79591.67)	19660.16 (-42925.26, 80366.48)	11692.17 (-47043.64, 76164.52)	112100.05 (14823.79, 205399.15)	13488.85 (-46429.99, 78461.71)	11320.93 (-69395.06, 76256.01)	15464.42 (-42381.85, 73697.51)
Alemtuzumab	70552.85 (-9314.54, 164282.34)	68569.57 (-18776.49, 154032.06)	66631.58 (-46114.83, 186765.71)	71752.67 (-39818.04, 169711.83)	73523.55 (-38842.81, 172125.37)	73528.34 (-39303.79, 171375.93)	65293.77 (-28120.24, 161792.09)	69583.85 (-51668.33, 159573.24)
Cladribine	67000.17 (-1139.26, 150009.19)	47925.74 (-15758.85, 115144.07)	64038.76 (-32928.61, 166013.22)	63343.28 (-30946.83, 142026.83)	65113.63 (-29954.22, 144216.84)	65157.75 (-29990.66, 143962.06)	61586.01 (-35184.55, 144023.09)	63197.03 (-30339.32, 149319.90)
Ponesimod	53859.04 (5779.06, 99977.03)	45417.84 (-4986.66, 109487.63)	52361.89 (-22244.03, 125652.46)	52914.78 (-21367.68, 127407.75)	54682.36 (-20094.45, 129871.31)	54642.10 (-19989.83, 128998.62)	NA	50485.35 (-34032.96, 103687.64)
Ofatumumab	11019.85 (-16076.43, 35701.92)	11392.17 (-43527.36, 73438.46)	9101.42 (-81547.54, 71661.17)	4542.80 (-50682.42, 61640.90)	6305.94 (-49455.46, 63754.93)	6447.23 (-49272.63, 65224.82)	NA	5965.65 (-64148.91, 66594.07)

Treatment	Base case	Scenario 1 (All RRMS MS Registry population)	Scenario 2 (base-case w/ random effects NMA)	Scenario 3 (base-case & assuming JCV testing provided free of charge by manufacturers)	Scenario 4 (using lowest price generics for comparators)	Scenario 5 (base case & assuming a reduction in Natalizumab-SC administration costs)	Scenario 6 (base-case w/ HA RRMS fixed effects NMA)	Scenario 7
Ocrelizumab	-1756.50 (-32266.54, 24285.25)	6083.57 (-54760.01, 76072.39)	2436.73 (-53964.77, 63208.69)	1182.58 (-54514.66, 54166.99)	2955.77 (-52789.89, 56044.66)	2855.42 (-52497.13, 55773.34)	-1692.38 (-55521.89, 66379.70)	-799.92 (-59031.30, 67011.13)
Peginterferon-beta-1 SC 125µg	115623.81 (50564.10, 186451.39)	105909.53 (44777.06, 162447.26)	113451.30 (33505.51, 196675.44)	111694.15 (25988.13, 194708.74)	113456.24 (27049.32, 196924.29)	113492.07 (25861.49, 196845.89)	109663.65 (32429.07, 196701.79)	113297.31 (26322.42, 206200.06)
Interferon-beta-1a SC 22µg	101661.76 (41745.72, 169892.42)	93804.93 (27077.84, 172572.88)	95988.16 (22092.04, 176099.78)	99565.28 (15283.09, 175195.96)	101340.58 (16254.93, 177498.18)	101239.97 (16481.05, 176715.60)	97066.81 (11614.41, 168362.09)	101543.98 (17951.11, 164857.78)
Interferon-beta-1a SC 44µg	107310.59 (40296.34, 181737.90)	95889.64 (29493.56, 173368.99)	104546.70 (-3285.31, 185018.90)	103305.46 (11909.60, 196222.80)	105062.85 (12899.75, 198502.25)	105210.97 (12585.65, 198123.52)	107545.64 (27665.19, 208223.99)	99881.53 (5734.23, 184926.69)
Interferon-beta-1a IM 30µg	99350.52 (35020.88, 172631.09)	87881.04 (17732.45, 162731.29)	91789.77 (-799.46, 167486.12)	94649.83 (15470.52, 195217.83)	96408.31 (16410.50, 197415.81)	96494.53 (15649.24, 197020.17)	101106.66 (7111.15, 185677.62)	98568.26 (4621.29, 180172.81)
Interferon-beta-1b SC 250µg	105408.97 (33814.12, 184712.12)	93156.95 (27895.51, 156339.77)	110847.20 (19936.40, 199364.12)	102232.50 (21434.50, 171463.58)	104004.44 (22284.72, 173594.21)	104089.61 (22371.04, 175048.28)	NA	101259.94 (5924.89, 172003.94)
Glatiramer Acetate 20mg	113389.31 (43692.80, 187217.79)	101473.55 (40585.57, 165634.60)	111954.69 (15074.72, 204471.72)	111624.42 (8862.28, 187008.85)	117031.53 (12231.88, 194810.43)	113375.10 (10068.09, 189150.07)	NA	112793.31 (16387.07, 193357.11)
Glatiramer Acetate 40mg	112915.58 (47344.46, 188242.01)	103574.85 (25064.64, 167350.25)	115017.85 (34471.32, 208709.69)	111996.24 (29943.39, 205073.47)	117376.09 (33576.76, 212377.89)	113757.96 (30444.69, 207861.01)	NA	109898.14 (15011.62, 191191.23)

6.8.5 Value of information analysis

The results of the value of information analysis are presented in Table 37. These show that the EVPPI is greatest for the NMA treatment effects on efficacy (ARR and CDP6) and safety (SAEs and discontinuation). This indicates that the greatest decision uncertainty is associated with the NMA estimates and RCT data. Utilities have a greater EVPPI than costs but both are important factors with a high EVPPI relative to total EVPI. Baseline rates of EDSS increase/decrease, progression to SPMS, and relapse rates have high and similar EVPPI. Absolute discontinuation rate and SAE rate have low EVPPI and their uncertainty thus has limited impact on the decision.

Table 37 Value of Information analysis results for the HARRMS base case using BART* method (publicly available list prices)

Parameter group	Per-person EVPPI at £20,000/QALY	Per-person EVPPI at £30,000/QALY
Total EVPI	8023.66	8985.47
NMA on CDP6	5966.55	6313.04
NMA on ARR	6005.47	6318.98
NMA on SAEs	5383.41	5629.18
NMA on discontinuation	5854.56	6171.58
Costs	3669.85	3061.73
Utilities	4712.21	4811.31
MS registry EDSS increase/decrease	3330.83	2693.98
MS registry SPMS progression	3051.01	2515.00
MS registry ARR	3089.55	2486.53
Discontinuation rate	1018.96	367.12
SAEs rate	1052.14	417.71

*BART=Bayesian additive regression trees

6.8.6 Summary of findings of economic evaluation

With the exception of ocrelizumab, all treatments had greater net benefit at £20-30,000/QALY than natalizumab-IV, natalizumab biosimilar-IV and natalizumab-SC. The natalizumabs also had close to 0% chance of having highest net benefit at £20,000/QALY and £30,000/QALY. Costs were generally higher on natalizumab than other treatments, though there was no difference in QALYs with 95% CrI completely overlapping.

Natalizumab-IV has lower mean net benefit at £20-30,000/QALY than natalizumab biosimilar-IV, although the 95% CrI overlap. Natalizumab-SC has very similar mean net benefit to Natalizumab-IV. The natalizumab biosimilar-IV has lower costs but also lower QALYs than natalizumab-IV but the 95% CrI for both are overlapping suggesting no evidence of a difference. Natalizumab-SC has very similar costs and QALYs to natalizumab-IV, again with no evidence of a difference.

Across all treatments, glatiramer Acetate 20mg and 40mg have the greatest net monetary benefits at £20-30,000/QALY, followed by interferon-beta-1a SC 44µg and interferon-beta-1b SC 250µg. However, the probability that any one of them has the greatest net benefit is below 25%, indicating high uncertainty as to which is most cost-effective.

Results were robust to sensitivity analyses relating to MS registry baseline estimates, use of random effects NMA, use of HA RRMS NMA, excluding the price of JCV testing for branded natalizumab, reducing the natalizumab-SC treatment administration costs, and stratifying mortality by EDSS severity. In the sensitivity using the HA RRMS NMA, glatiramer acetate and Interferon-beta-1b SC 250µg were not included. However, natalizumab-IV and natalizumab-SC were not cost-effective compared to any included treatment and the most cost-effective treatment was peginterferon -β-1 SC 125µg.

Value of information analysis found that the parameters with greatest impact on the results were the NMA hazard ratios on ARR, CDP6, SAEs, and discontinuation. However, many parameters, including costs, utilities, and MS registry rates, had substantial impact on the results indicating high parameter uncertainty.

7 Assessment of factors relevant to the NHS and other parties

New diagnostic criteria for MS reported at the recent ECDMS conference may allow earlier diagnosis, and hence also treatment, of people with MS. This will have implications for the NHS. The lack of a consensus definition on HARRMS make it challenging to introduce treatments for this population. There is a need for a clear and consistent definition of the HARRMS population to allow treatments to be prescribed appropriately.

Evolving formulation availability will affect delivery options and some Trusts may make decisions based on support from pharmaceutical companies. For example, in-home delivery of infusions by nurses supplied by companies. However, this could raise a vulnerability with shifts in demand if these are subsequently withdrawn, particularly if done at relatively short notice.

8 DISCUSSION

8.1 Statement of principal findings

Based on findings from our NMA and SLR, most interventions reduced relapses and the proportion of participants with MRI lesions compared to placebo. Alemtuzumab, ocrelizumab, natalizumab, fingolimod and peginterferon beta 1a also reduced disease progression compared to placebo. There was no differences in any AEs, serious AEs or treatment related AEs for any intervention compared to placebo. Fingolimod, glatiramer acetate, interferon beta 1a, interferon beta 1b and peginterferon beta 1a were associated with increased treatment discontinuation. There was little evidence for a difference in quality of life. There was no evidence of a difference between natalizumab and natalizumab biosimilar for relapse rates, MRI lesions or AEs. Data in HARRMS were available for fingolimod, ocrelizumab, alemtuzumab, cladribine, beta-interferon, AHSCT, and placebo. We also included one study on natalizumab conducted in a population that was close to our definition of HARRMS. All interventions except interferon beta 1a were associated with reduced relapse risk compared to placebo; there were little data for other outcomes.

Compared with natalizumab-IV, natalizumab biosimilar-IV and natalizumab-SC, all treatments had greater net benefit at £20-30,000/QALY, with the only exception being ocrelizumab which had lower net benefits. Costs were generally higher on natalizumab than other treatments, though there was no difference in QALYs with 95% CrI completely overlapping. The results and conclusions were unchanged under all sensitivities. Value of information analysis found that the greatest contributor to decision uncertainty was the effectiveness of treatments.

8.1.1 Findings on clinical effectiveness

We identified 42 studies that fulfilled inclusion criteria for our SLR. However, the majority of the evidence was in the general RRMS population rather than those with highly active disease, and most studies evaluated comparator interventions rather than the technologies of interest for this appraisal - natalizumab (Tysabri, Biogen) and natalizumab biosimilar (Tyruko, Sandoz).

ARR was the most frequently reported outcome across studies, with 39 of the 40 trials in the general RRMS population reporting data for this outcome. ARR data generally suggested that newer DMT, such as alemtuzumab, ocrelizumab, and natalizumab, are more effective than older treatments like interferon beta and glatiramer acetate, which showed limited improvements over placebo. Fewer than half the included studies provided data on the proportion of participants who had Gd+ (19 studies) or new or enlarging T2 lesions (17 studies) but data were consistent with the findings for ARR, suggesting a greater effect for newer DMT. Disease progression was also reported in less than half of studies, and we were unable to connect studies of teriflunomide, ponesimod, and ofatumumab to the main network. These studies were therefore not included in the NMA for these outcomes. Data for the remaining interventions were also consistent with the findings for ARR, suggesting a

greater effect of newer DMT on reducing disease progression, with slightly stronger evidence on an effect for CDP3. Disability progression can be highly variable across individuals, with some showing gradual decline followed by periods of improvement rather than consistent decline over relatively short time periods, with decline only becoming evidence over longer time periods. This can make it difficult for patients to meet the criteria for confirmed disability progression, particularly CDP6 which requires sustained progression over 6 months, over shorter follow-up periods (e.g., 6 months). The use of sustained disability metrics, such as 6-month confirmed disability progression (CDP6), offers a more reliable measure of true progression than CDP3, as it reflects long-term changes rather than temporary fluctuations. However, true disability progression often unfolds over years or even decades, making it challenging to observe in standard clinical trials with shorter follow-up periods.[171, 172]

All but two of the trials included in this review provided data on AEs, a further two only reported data on specific AEs of interest and so could not be included in our synthesis as they did not report at least one the AEs measures of interest for this appraisal (incidence of any AEs, SAEs, treatment related AEs, of treatment discontinuation due to AEs). There was no evidence of an increased risk of any AEs or treatment related AEs for any of the interventions evaluated. It may be difficult to determine the true impact of AEs from the outcome "any AE" as this is defined very broadly so that any potential adverse events, including those not thought to be related to the intervention, are recorded as potential AEs. Close to 100% of participants in both groups experienced AEs and so this measure does not distinguish between groups. There were less data on treatment related AEs which were only reported for eight studies. These may be expected to be a more appropriate measure of the true risk of AEs associated with the different interventions, but there was also little evidence of a difference between groups for this measure. There was a suggestion that natalizumab and peginterferon beta 1a were associated with a lower risk of SAEs compared to placebo, but CrIs were wide and included 1. Fingolimod, glatiramer acetate (SC20), interferon beta 1a (SC44) and peginterferon beta 1a were associated with a higher rate of treatment discontinuation than placebo; there was no evidence of a difference between other interventions and placebo. However, SAEs are generally rare and so require large sample sizes to show difference in risk between groups. Analyses of real-world data may be necessary to identify the potential risk of these.[173]

There was limited evidence on the technologies of interest for this appraisal - natalizumab and natalizumab biosimilar. We identified only four studies of these interventions. This included two placebo control trials of natalizumab – AFFIRM, a large multinational trial (n=943) with 24 months follow-up, and Saida 2017 which only included 94 participants, had a short follow-up period of 6 months and only included Japanese participants. An additional trial (REVEAL) compared natalizumab with fingolimod. This phase 4 randomised study, with a planned overall duration of 68 weeks was terminated prematurely due to slow enrolment and so data were only available for 12 months follow-up. The fourth trial was a direct comparison between natalizumab and natalizumab biosimilar – the only randomised

evidence available for this intervention. This trial also had a short follow-up period (24 weeks) and its primary outcomes were MRI findings (new gadolinium-enhancing T1-weighted lesions and new/enlarging T2-weighted lesions). However, two previous meta-analyses [174, 175] have found a correlation between the effect of MS drugs on relapses and MRI activity, with the magnitude of the benefit on MRI lesions predicting the magnitude of the effect on relapse rates. All four trials were conducted in the general RRMS population and did not provide any data specifically in patients with HARRMS. However, the Saida 2017 study included a very high proportion (88%) of previously treated participants and required that participants had experienced at least one relapse in the preceding year, and so was close to our definition of at least 90% of participants having HARRMS. Overall, the available data suggested no evidence of a difference between natalizumab and its biosimilar in terms of annualized relapse rate (ARR), the proportion of participants with MRI-detected lesions or AEs. There were no data on disease progression for patients treated with natalizumab biosimilar, although natalizumab was associated with a greater reduction in CDP3 and CDP6 compared to placebo.

All trials of natalizumab evaluated natalizumab administered intravenously - there were no studies of natalizumab administered subcutaneously. We did not identify any studies that compared subcutaneous administration of natalizumab with another intervention of interest for this appraisal. We are aware of a small number of trials that have compared different modes of administration of natalizumab, but none met inclusion criteria for our review. DELIVER[176] compared the pharmacokinetics and pharmacodynamics of single subcutaneous or intramuscular 300 mg doses of natalizumab with IV 300 mg doses in patients with MS with a short follow-up duration of 24 weeks and REFINE[177] compared switching to different dosing regimens in stable patients with RRMS who were treated with natalizumab. This study did not meet inclusion criteria for our review as all participants were already receiving natalizumab. These two studies found that natalizumab administered as a 300 mg SC injection every 4 weeks was comparable to 300 mg IV infusion natalizumab every 4 weeks in terms of ARR and CDP3 at week 60 as well as for pharmacokinetics, pharmacodynamics, and safety outcomes.

We only identified 6 trials that provided data on people with HARRMS. Two studies (MIST, and CARE-MS II) were conducted exclusively in people with HARRMS, and four reported data for a subgroup of participants with HARRMS – this included two sets of related trials that provided pooled results for the highly active subgroup. We also included the Saida 2017 trial in our synthesis of data on people with HARRMS as it was close to fulfilling our criteria of a “highly active population”. However, it should be noted that this study was restricted to Japanese patients and so results may not be generalisable to the UK population. Comparison of baseline characteristics between these populations suggested that those with highly active disease had fewer relapses as baseline, possibly as they had all been treated with DMTs in the previous year, and generally slightly worse EDSS scores. The only outcome with sufficient data to conduct an NMA for this population was ARR. To enable us to connect the network for this analysis we had to assume a class effect for interferon beta

1a (Interferon beta 1a IM30 and interferon beta 1a SC44). The findings from this analysis were very similar to the findings in the overall RRMS population. To allow direct comparison of findings between these two populations we conducted an NMA for the general RRMS population restricted to the interventions for which data were available in the HARRMS population (alemtuzumab, ocrelizumab, fingolimod, cladribine and natalizumab). Results were very similar across the two populations, although with wider credible intervals for the HARRMS population. This would be expected as there were less studies and less patients contributing to this analysis. Although we could not carry out an NMA for disease progression, we presented results for the highly active and general RRMS populations in a table to allow direct comparison between populations. This suggested that estimates were similar, with HRs generally slightly lower (i.e. suggesting a greater effect) in the highly active population, but again with wider confidence intervals. Data on adverse events and quality of life were only reported in the CARE-MS I study and so it was difficult to draw conclusions regarding the impact of DMT on these measures in the HARRMS population.

In addition to the data from RCTs in people with HARRMS, there is some evidence from non-randomised studies on the effectiveness of natalizumab in people with HARRMS; these studies were not included in our SLR and NMA as our inclusion criteria specified that only RCTs were eligible. A recent targeted literature review and meta-analysis of natalizumab for the treatment of highly active RRMS[178] included studies in adults (≥ 18 years) with a confirmed diagnosis of RRMS who had an unchanged or increased relapse rate compared with the previous year, failed to respond to a full and adequate course of disease modifying therapy (DMT), and had experienced at least one relapse in the previous year while on therapy. They included 16 non-randomised studies that compared natalizumab to interferon beta, glatiramer acetate, teriflunomide, dimethyl fumarate and fingolimod and 11 case series of people treated with natalizumab. Data in the HARRMS population are also available for the TOP study, the largest real world study of natalizumab, that evaluated the long-term safety and efficacy of natalizumab in 6321 patients (134 UK patients) with RRMS with a follow-up pf 15 years. [151] A post-hoc subgroup analysis in a subset of patients with HARRMS, defined as those who had received prior treatment with ⩾1 DMT and had experienced 1 relapse reported similar findings to the findings in the general RRMS population of a reduction of over 90% compared to the year before starting natalizumab. These findings support natalizumab improving outcomes for patients with RRMS and HARRMS, but do not provide a comparison with other interventions.

Overall, the very limited data suggest that interventions evaluated in people with HARRMS are at least as effective in this population as they are in the general RRMS population, but this should be interpreted with some caution due to the very small number of studies for which data were available in patients with HARRMS.

8.1.2 Findings on cost-effectiveness

Our systematic review of existing cost-effectiveness evaluations found seven studies for inclusion. None of these answered our decision problem of evaluating the cost-effectiveness

of natalizumab and natalizumab biosimilar relative to standard of care in our target population of HARRMS after at least one disease modifying therapy. We therefore undertook an independent economic assessment.

To design the model we reviewed models used in previous relevant TAs. These were essentially the same Markov multistate model based on EDSS severity level with baseline transition rates informed by the British Columbia Multiple Sclerosis registry and London Ontario MS databases and treatment effects by individual trials and NMA. Primary criticisms of these models were that they did not capture treatment sequencing and that they were unable to accurately reflect the course of the condition. We aimed to overcome these limitations by using a DES microsimulation that allowed the modelling of treatment sequences, similar to a recent microsimulation for the Dutch RRMS guidelines. [138-141] Our model included attributes for age, sex, EDSS, SPMS status and current treatment. It modelled the events EDSS increase, EDSS decrease, progression to SPMS, relapse, SAEs, treatment discontinuation, and death. Patients could switch treatment twice, meaning that up to 4th line therapy was included in the model. It furthermore modelled patients who progressed to SPMS with events of EDSS increase, relapse, SAEs, and death.

Event rates were a combination of natural history informed by analyses conducted by the UK MS Registry and treatment effects of ARR and CDP6 informed by the NMA. The clinical review found no evidence on AHSCT so this was not included in the economic model. Baseline SAEs and discontinuation came from AFFIRM and ANTELOPE with treatment effects from the NMA. Event rates in the SPMS population were informed purely by the MS Registry analyses as no treatment effects were assumed. Our approach to costs and utilities were aligned with previous TAs. The economic model was implemented in the R programming language using the DESCEM package.[179] The code was validated by the DESCEM develop Javier Sanchez Alvarez at Evidera.

A validation against EDSS progression over time from an earlier Markov model found that the trend predicted by the economic model was for lower increase in severity.[126] However, the earlier model was in a mixture of RRMS and SPMS and did not include the latest DMT sequences, so would be expected to have a worse prognosis. Convergence tests found the model to give stable results with greater than 100 patients and 100 samples.

Compared with natalizumab-IV, natalizumab biosimilar-IV and natalizumab-SC, all treatments had greater net benefit at £20-30,000/QALY, with the exception of ocrelizumab. The natalizumabs also had close to 0% chance of having highest net benefit at £20,000/QALY and £30,000/QALY. Costs were generally higher on natalizumab than other treatments, though there was no difference in QALYs with 95% CrI completely overlapping. Natalizumab-IV has lower mean net benefit at £20-30,000/QALY than natalizumab biosimilar-IV, although the 95% CrI overlap. Natalizumab-SC has very similar mean net benefit to Natalizumab-IV. The natalizumab biosimilar-IV has lower costs but also lower QALYs than natalizumab-IV but the 95% CrI for both are overlapping suggesting no evidence

of a difference. Natalizumab-SC has very similar costs and QALYs to natalizumab-IV, again with no evidence of a difference.

We conducted sensitivity analyses testing robustness switching to All RRMS estimates from the MS Registry, switching to use of random effects NMA, using the HA RRMS NMA, excluding the price of JCV testing for branded natalizumab, reducing the natalizumab-SC treatment administration costs, and using mortality stratified by EDSS severity. The results and conclusions were unchanged under all sensitivities. Our estimates of the EVPPI in value of information analysis found that the parameters with greatest impact on the results were the NMA treatment effects on ARR, CDP6, SAEs, and discontinuation. However, many parameters, including costs, utilities, and MS registry rates, had substantial impact on the results indicating high parameter uncertainty.

8.2 Strengths and limitations of the assessment

8.2.1 Systematic review and NMA strengths and limitations

Our systematic review followed published guidance on the conduct of systematic reviews,[46, 47] and network meta-analysis[47] and is reported according to PRISMA-2020[48] and PRISMA guidance for NMA[49] making our review processes transparent and robust. The protocol was pre-registered on the PROSPERO database (PROSPERO 2024 CRD42024556838).[180] Changes to the protocol are clearly described in Section 4.4. Protocol changes were either to clarify issues that were ambiguous in the original protocol or to focus the review to make this manageable within the resources and time available. We clarified the inclusion criteria in relation to interventions, limiting inclusion so that only those evaluated at doses currently licensed in the UK were eligible for inclusion. This ensured that findings would be directly relevant to the UK population. Due to time and resource constraints, we focused on the following outcomes: relapse rates, proportion of participants with Gd+ and T2 weighted lesions on MRI scans, disability progression, adverse events and health-related quality of life measured using EQ-5D or SF-36. This means that we did not consider severity of relapses or symptoms of multiple sclerosis (such as fatigue , cognition, and visual disturbance) that had been specified as eligible in our protocol. These outcomes were reported inconsistently across included studies using a variety of different outcome measures and so it is unlikely that sufficient data would have been available in a consistent format to allow us to conduct an NMA for these outcome measures. Focusing on our two specific MRI measures (proportion of participants with Gd+ or new or enlarging T2 lesions) means that we were not able to considered other MRI measures such as brain lesion volume which has been proposed as a better marker of disease progression than clinical measures such as CDP6.[181]

We conducted extensive literature searches designed to maximise retrieval of relevant studies and did not apply any language, date or publication restrictions to these searches or to inclusion in the review. Four reports considered potentially relevant for inclusion and reviewed at the full text stage were reported in non-English language. We used Google Translate to assess these against our inclusion criteria and determined that none met our eligibility criteria. We pre-specified clearly defined, objective inclusion criteria. Although the

population of interest for our appraisal was those with HARRMS, we defined broad inclusion criteria so that studies in any RRMS population were eligible for inclusion. We also applied a broad definition for highly active disease to include any "unchanged or increased clinical or radiological evidence of disease activity despite treatment with at least one Disease Modifying Therapy (DMT)" – this broad definition ensured that any data in a population that could be considered to have highly active disease based on definitions used in trials would be eligible for inclusion. As no data were available for natalizumab for this population, we further broadened eligibility criteria to include the Saida 2017 study that had a high proportion of patients who had been previously treated and used this as a proxy for highly active disease. This allowed us to include natalizumab in our NMA for ARR for people with HARRMS. We screened TAs that had evaluated any of the interventions or comparators of interest for this appraisal to identify additional studies and data that were relevant to the review but were not reported in publications of the trials. This allowed us to include additional data than had we only included data available in publications or clinical trial registries. We clearly report all publications and TAs related to each included study in Appendix 2, and document whether data were extracted from each report. Some of the TAs included redacted information that appeared relevant to our review but could not be included as we did not have access to this information. Data that could not be accessed that may have been informative to our review were:

- TRANSFORMS (TA254): baseline data on relapses and EDSS scores and hazard ratios for HARRMS, and EQ-5D data for general population.[40]
- CAMMS 223 (TA312): redacted QoL data – unclear what measures were reported.[39]
- OPTIMUM (TA767) – some data in HARRMS but unclear exactly what outcomes reported as full table redacted.[42]
- ASCLEOPIOS I and II (TA699) – ARR, CDP3 and CDP6 for HARRMS.[41]

These data may have allowed us to include TRANSFORMS in the analysis for disease progression in the HARRMS population – this study was included for the ARR synthesis in people with HARRMS. OPTIMUM and ASCLEPIOS I & II did not report data for the HARRMS subgroup and so these data may have allowed us to include these studies for this population. However, both studies were only included to connect the network as teriflunomide was not listed as a comparator for this appraisal and so these data would only have been helpful if their inclusion created additional connected networks for the HARRMS population. In addition, the definition of HARRMS for the ASCLEPIOS studies differed from our definition as it included people previously treated with DMT who discontinued DMT due to lack of efficacy – relapses were not part of the definition. The data on QoL for TRANSFORMS and CAMMS 223 could have provided additional useful data on QoL that was rarely reported in studies included in our review.

We conducted a formal assessment of the risk of bias of included studies using the RoB 2 tool for RCTs,[55] the only tool for the assessment of risk of bias in RCTs recommended as a key tool by the LATITUDES Network.[182] Risk of bias was performed at the outcome level as recommended, the importance of following this approach was shown by the fact that for

some trials risk of bias judgements differed for the different outcomes. We incorporated the risk of bias into the synthesis for ARR, the only outcome for which sufficient data were available, by conducting a sensitivity analysis restricting the analysis to studies at low risk of bias. This produced very similar results to the overall analysis suggesting that risk of bias did not impact on findings for this outcome. For all outcomes, we included the risk of bias in results tables to allow readers to qualitatively judge whether risk of bias may have impacted on study findings.

We used a new software package, Nested Knowledge, to manage the different stages of the review process. We found that this improved the efficiency of the review process and management of the review, and facilitated creation of tables for analysis and inclusion in the report. This reduced the risk of errors when exporting and manipulating data.

We employed Bayesian Network Meta-Analyses (NMA) to compare the efficacy and safety of treatment options using trial data, enabling simultaneous evaluation of multiple interventions. NMA strengthens inferences by combining direct and indirect comparisons while maintaining randomisation, making it especially useful for reviews such as our when most treatments lack head-to-head RCT comparisons. This systematic review assessed key outcomes to evaluate disease-modifying therapies (DMTs) for multiple sclerosis (MS), offering a comprehensive comparison across various domains of safety and effectiveness. Unlike previous reviews, we included studies with follow-up durations under 12 months, expanding the scope of data analysed and integrating follow-up time into calculations to account for treatment exposure. Unlike prior pooling by timepoint, all timepoints were included in a single analysis allowing us to create a more comprehensive network, as evidence from previous reviews has suggested no significant variation in rates across timepoints. [183, 184] Additional analyses on confirmed disability progression (CDP) utilised both the CDP3 and CDP6 networks, facilitating broader comparisons between interventions. The inclusion of recently published studies ensured up-to-date data on several treatments, while analysing drugs and doses as individual nodes allowed for precise comparisons. Model selection (random- or fixed-effects) was determined based on heterogeneity and Deviance Information Criterion (DIC) values to ensure optimal fit for each analysis. Minimal heterogeneity was observed for key outcomes, including annualised relapse rate (ARR), CDP3, adverse events (AEs), and MRI outcomes, with fixed-effect models providing better data fits in these cases. The exception was CDP6 where the random effects-model provided a better fit to the data.

Our network meta-analysis (NMA) focused on interventions identified by NICE as being within the scope of this appraisal. This may have excluded some relevant treatments that are recommended for the general RRMS population but not for the HARRMS population, including dimethyl fumarate, diroximel fumarate and teriflunomide. Whilst we included studies that compared teriflunomide with interventions and comparators in scope for this appraisal, we did not expand our searches to identify studies that compared teriflunomide against other treatments such as placebo due to time and resource constraints. As

teriflunomide was not identified as a comparator for this appraisal as it is not recommended for people with HARRMS, we were not aiming to provide recommendations on its effectiveness. Results for teriflunomide should therefore be interpreted with caution.

Where we calculated hazard ratios (HRs) for confirmed disability progression (CDP3 and CDP6), proportion of participants with lesions on MRI scans, and adverse events, we assumed constant HRs over time. This may not be a valid assumption, but data were not available to allow other methods of estimation. Variability across studies in definitions, follow-up times, and baseline characteristics posed challenges, though clinicians confirmed these differences were reasonably comparable. The analysis of the HARRMS population was further constrained by inconsistent definitions and data gaps for several interventions, introducing potential heterogeneity. Finally, the limited number of studies for each individual intervention restricted sensitivity analyses, potentially impacting the robustness of certain conclusions.

Many reviews have evaluated the safety and/or efficacy of treatments for MS in the past 5 years.[183-194] We did not include existing reviews in our review, but we screened the included trials from recent reviews (published in past 3 years) against our review inclusion criteria to ensure that we had not missed any relevant studies. The only study included in an existing review that met our inclusion criteria but had not been included in our review was reported only in a conference abstract – we were unable to retrieve the full text of this study.[66] Most previous reviews focus only on one or two specific outcomes, for example ARR and CDP[192, 195] for adverse events,[193] or on specific interventions such as cladribine[191] or ocrelizumab.[183] The results of our review are consistent with those from other recent reviews that have included a broadly similar set of interventions, with very similar estimates of effect for ARR.[192, 195] The exception was for teriflunomide, with estimates from our review suggesting that this is less effective than found by other reviews. This may be because they differed in eligibility criteria for interventions, including all studies of teriflunomide including those compared to placebo. In contrast, we only included studies of teriflunomide to allow us to fully include ocrelizumab in our network. Teriflunomide itself was not specified as a comparator for our review. Previous reviews[183-194] have mostly focused on interventions for people with RRMS. We are only aware of one previous systematic review [196] in the HARRMS population. This review only included 2 studies comparing fingolimod and dimethyl fumarate with placebo. Our review is therefore the first to provide a comprehensive overall assessment of the effectiveness of our specified interventions and comparators in this population.

Limitations of the evidence base

The risk of bias (ROB) varied across studies and outcomes, with around half of studies judged at low ROB overall. No studies were classified as high ROB for the randomisation domain, although 14 studies were rated as having "some concerns" due to insufficient information on randomisation or allocation concealment but with no evidence of baseline imbalance. Five studies were at high ROB due to participants being aware of interventions

and evidence of differential withdrawal across treatment groups. Another five unblinded studies showed no deviations from intended interventions and were judged at "some concerns." High ROB was observed in several trials due to a high proportion of withdrawals potentially linked to the intervention as worse outcomes could be associated with a greater likelihood of withdrawing. Six studies were rated as high ROB for missing outcome data for relapse rates with an additional eight rated high ROB for missing MRI data. There was little suggestion of missing data for adverse events, which were reported for most participants in the included trials. Although most studies used an ITT or modified ITT analysis to include all randomised participants in the analysis, few detailed the methods used for estimating outcomes for participants without follow-up data. Two studies were rated high ROB for outcome measurement due to unblinded assessors, and 14 studies had "some concerns" for selective outcome reporting, as protocols were unavailable or outcomes were inconsistently reported. We conducted a separate ROB assessment for the trials that reported data in people with highly active disease. We did not consider this to change the risk of bias for the randomisation domain, as whether or not participants had highly active disease was determined at baseline and so could not be influenced by treatment. This means that we would expect randomisation to result in equivalent groups in this sub-population.

8.2.2 Economic model strengths and limitations

We developed a novel economic model for highly active RRMS that built on the evidence and assumptions of previous NICE TAs but extended to a flexible DES approach that enabled the modelling of treatment sequences. The baseline rates of EDSS increase, EDSS decrease, relapse, and progression to SPMS were informed by a new analyses of the UK MS Registry, aligning with our target UK highly active RRMS population. Treatment effects on disability progression, relapse, adverse events and discontinuation were estimated using the high quality NMA on randomised controlled trial evidence, although it was necessary to use the all RRMS population as few trials were identified for highly active RRMS. The DES modelled disease that has progressed to SPMS, capturing the disease course beyond RRMS. A large number of treatment comparators were included, representing possible standard of care in highly active RRMS. The model was fully probabilistic with parameter uncertainty propagated from the input evidence to the final results, and considered in interpretations. Validation against published data found differences in EDSS trend over time that could be explained by the comparator model mixing RRMS and SPMS patients and not including patients on the latest DMT sequences. Convergence tests found that results became stable with only a low number of patients and samples. Finally, value of information analysis was used instead of deterministic one-way sensitivity analysis. This considers the uncertainty in all parameters simultaneously, rather than varying parameters one at a time. Unlike deterministic sensitivity analysis, it measures a parameter as important if its uncertainty can change the decision (i.e., switch an incremental net benefit from positive to negative and vice versa) rather than only changing the net benefit or ICER themselves.

Despite the novelty and strength of evidence, the economic model also had substantial limitations. A key limitation is that treatment effects were informed by the NMA in all

RRMS, rather than being based on trials in highly active RRMS. Furthermore, there was no evidence identified on autologous haematopoietic stem cell transplantation so this was not included in the economic model.

Although we used new analyses of the MS Registry to inform baseline rates of events, these were based on small sample sizes which gave uncertainty estimates. The MS Registry found no patients with highly active RRMS who decreased in EDSS so analysis could not be conducted and EDSS decrease from the all RRMS population had to be used in all analyses. It was also not possible to use the multistate modelling approach due to unstable estimates of transition rates between low EDSS states.

Our model used constant SMRs rather than varying these with EDSS states. Previous appraisals (e.g., TA767) have modelled relative risk of death being applied to each EDSS health state, taken from Pokorski (1997) but these data are considerably out of date and no replacement was identified.[42] Despite it being possible using discrete event simulation, we did not consider capacity constraints, for example with limited availability of MRI machines. Treatment stopping rates were assumed constant over time, rather than being higher in the first year of treatment than in subsequent years, which was recommended by the EAG in TA616.[38] This flexibility is possible but the NMA on discontinuation due to AE did not have sufficient data to vary rates by year since treatment initiation. The validation was limited to EDSS change over time. No suitable data were identified for a deeper validation of relapse rates and EDSS distributions.

8.3 Uncertainties

The key uncertainty remaining is whether treatment effects vary between those with RRMS and those with HA disease. There were insufficient data in people with highly active disease to fully answer this question. There was also very limited data on natalizumab biosimilar and so there is also some uncertainty in whether this is equivalent in effectiveness to natalizumab, and on whether either of these interventions is effective in those with highly active disease. This uncertainty is also key to the cost-effectiveness conclusions as the model assumed that treatment effects would not vary between those with RRMS and those with HA disease.

There were differences across studies in how outcomes, particularly relapse rates and disease progression were defined. There were insufficient data to investigate whether these differences affected estimates of treatment effect. Previous research has suggested that different ways of measuring disability may affect estimates of treatment effect.[197] There was also inconsistency in how studies defined “highly active disease”. Future studies should also adopt a consistent definition.

Another key uncertainty is whether it is reasonable to assume that treatment effects remain stable over time. The economic model assumed that treatment effect were stable long-

term, despite this uncertainty. For our analysis, we combined data from studies with different durations of follow-up ranging from 6 to 24 months, although most studies reported outcomes at 24 months follow-up. We had intended to conduct a sensitivity analysis to investigate whether results were different when analysed at different time points, but there were insufficient studies that reported results at 6 and 12 months follow-up for this to be possible. Three studies (AFFIRM, IFNB study and PRISMS) reported data at both 12 and 24 months follow-up. These studies reported similar estimates of ARR at the different follow-up times suggesting no difference in effect, but it was unclear whether those with 6 months follow-up would have different findings. Five studies only reported short duration of follow-up of less than 12 months (range 4 to 9 months). It may not be reasonable to expect consistency over time in MRI outcomes – our clinicians advised us that they would be less concerned about new lesions that develop within the first 6 to 12 months of treatment but would be more concerned with lesions after longer treatment duration. AEs may also differ in effects and timing depending on the specific interventions. For example, for some drugs like alemtuzumab and cladribine effects may be expected to be front loaded whereas for others a more cumulative effect may be expected. These potential differential effects were not assessed in our review and so this remains an uncertainty of our findings.

The MS Registry analyses that were used to inform the economic model had low sample size for some events. Relapse rates in the highly active RRMS were based on only 50 patients while the rate of progression to SPMS was based on only 66 patients. Furthermore, it was not possible to estimate reliable multistate transition matrix so only exponential survival models could be used for EDSS increase and decrease events.

The results themselves are highly uncertain, in particular the total and incremental QALYs. The 95% CrI are completely overlapping for all treatments, meaning that differences in effectiveness cannot be established. These are themselves due to uncertainty in the clinical evidence from the MS Registry and NMA on trials in all RRMS. However, cost differences are large and 95% CrI more rarely overlap, which leads to the observed differences in net benefit. Value of information analysis ranked the parameters on their impact on decision uncertainty, from highest to lowest, as NMA treatment effects, MS Registry baseline rates, costs, utilities, rates of discontinuation, and rates of SAEs.

8.4 Patient and Public Involvement

We involved one patient representative with lived experience of MS in this project. They attended team meetings (one at the beginning of the project and one closer to the end of the project), gave feedback on the plain language summary report, and wrote the section below about the impact that these interventions may have on people with MS.

8.5 Impact on patients

Receiving a diagnosis of highly active relapsing-remitting multiple sclerosis (RRMS) can be a challenging and emotionally taxing experience. The nature of RRMS, with its unpredictable

relapses and potential for significant disability, often makes the journey to diagnosis complex and uncertain. While timely diagnosis is crucial, particularly for highly active cases, accuracy and careful tailoring of treatment plans are even more critical to ensure the best outcomes for patients. The period of waiting for a diagnosis or treatment can be overwhelming, highlighting the need for transparent communication and support throughout this process.

Advances in disease-modifying therapies (DMTs) have transformed the landscape of RRMS treatment, yet identifying the most effective and tolerable option for each individual remains a nuanced and sometimes lengthy process. Patients frequently report feeling underserved when it comes to monitoring treatment effectiveness or managing side effects. Improvements in these areas, supported by robust evidence and innovative tools, could significantly enhance care. Holistic, patient-centred approaches that prioritise early intervention, personalised treatment and psychosocial support are essential to improving quality of life for those living with RRMS.

8.6 Equality, Diversity and Inclusion

Our research was based on existing literature and so we had no control over the participants enrolled. We were broad in our inclusion criteria such that studies from any country and in any language of publication were eligible.

Our team included researchers with a broad range of experience and expertise. The lead authors are junior researchers within Bristol TAG, who were given the opportunity to lead on the writing of this report to help develop their research skills and portfolio. They were supported by the two senior authors, who provided advice and mentorship to the junior researchers leading on the reviews and health economic modelling. The team included those with expertise in systematic reviews, health economics, and medical statistics.

8.7 Implications for decision makers

There are insufficient data on natalizumab and natalizumab biosimilar in people with HARRMS. Limited evidence suggests that there is no difference in treatment effect between these interventions in people with RRMS. There is also a suggestion that other DMT have at least equivalent efficacy in people with highly active disease to that in people with RRMS. It may be reasonable to assume that this would also be the case for natalizumab and natalizumab biosimilar. The economic model made this assumption of equivalent efficacy in HARRMS as in the general RRMS and found that natalizumab and natalizumab biosimilar are unlikely to be cost-effective. These should therefore not be recommended for people with HARRMS.

8.8 Research recommendations

There is a clear need for more studies in people with highly active disease to determine optimum treatment recommendations. There is a lack of data on the efficacy of natalizumab

and natalizumab biosimilar, particularly in people with highly active disease. This was a key uncertainty in the economic model, as indicated by the value of information analysis. Further studies are needed of these interventions in people with highly active disease. Future studies should include at least 24 months follow-up to determine whether effects are sustained over a reasonable time frame. This is particularly important for assessment of disease progression, especially over longer periods of time such as CDP6. There is also a need for accepted definitions of HARRMS, relapses, and disease progression with MS. Future studies should use the same definitions to allow comparison across studies. Understanding of disease progression in HARRMS is also limited, as indicated by value of information analysis and low sample size in the MS Registry analyses. Further studies should additionally record utilities by EDSS severity and the disutilities associated of relapse and adverse events.

9 CONCLUSIONS

There were no data on the effectiveness of natalizumab or natalizumab biosimilar in patients with highly active disease. Limited data suggest that natalizumab and natalizumab biosimilar have similar effectiveness for people with RRMS population. Comparison of data on the effectiveness of DMT in people with highly active disease and those with RRMS suggest that DMTs evaluated are at least as effective in this population. However, this is based on very limited data. Assuming that natalizumab and natalizumab biosimilar follow this same pattern, it may be reasonable to assume that these interventions would also be effective in those with highly active disease. However, trials in this specific population are needed to confirm whether this is the case.

Based on the findings from the clinical review, the economic model made the assumption that treatment effects in the general RRMS population would apply to the HARRMS population and used these data and baseline rates from the MS Registry in highly active RRMS. All treatment had greater net benefit at £20-30,000/QALY than natalizumab-IV, natalizumab biosimilar-IV and natalizumab-SC, with the exception of ocrelizumab which had lower net benefits. The natalizumabs also had very low probability of having highest net benefit at £20,000/QALY and £30,000/QALY. There were no differences in costs, QALYs, or net benefit between the natalizumabs, with the 95% CrI overlapping. Analyses were robust to sensitivities and the greatest decision uncertainty was found in the treatment effects as estimated by the NMA. These findings suggests that natalizumab and natalizumab biosimilar are not cost-effective compared to standard of care in highly active RRMS but that further research is needed on the treatment effects.

10 Additional Information

10.1 Declaration of competing interests

Dr Claire Rice declares the following interests:

- Regular prescriber of Multiple Sclerosis (MS) disease modifying therapies in National Health Service (NHS) MS clinics.
- Work with the MS Society as an expert panel reviewer on grant applications.
- Research grant funded by Sanofi looking at blood biomarkers of people with MS.
- Routinely involved in clinical trials other clinical studies of people on disease modifying therapies for MS including natalizumab but these are investigator-led and are not commercial studies.

Dr Emma Tallantyre declares the following interests:

- Honorarium from Roche / Novartis for consulting work in the last 12m.
- Expenses for attending educational meetings from Merck.
- Biogen honorarium for speaker fees but not in the last 24m.

Howard Thom owns shares in Clifton Insight which has received consulting fees from Amicus, Argenx, Baxter, Bayer, Daiichi-Sankyo, Eisai, Janssen, Lundbeck, Merck, Novartis, Novo Nordisk, Pfizer, and Roche.

10.2 Contributions of authors

Catalina Lopez Manzano- Conceptualisation; data extraction and risk of bias assessment; network meta-analysis; project administration; writing – original draft; writing – reviewing and editing
Ayman Sadek- Conceptualisation; health economic modelling; project administration; visualisation; writing – original draft; writing – reviewing and editing
Chris Cooper – Literature searches and health economics review; writing – original draft
Eve Tomlinson – Data extraction; writing – reviewing and editing
Hanyu Wang – Data extraction; writing – reviewing and editing
Claire Rice - Writing – reviewing and editing; other – clinical advice
Emma Tallantyre - Writing – reviewing and editing; other – clinical advice
Ananya Rao-Middleton - Writing – reviewing and editing; other – PPI contributions
Penny Whiting – Conceptualisation; formal analysis; funding acquisition; methodology; investigation; project administration; supervision of systematic review; visualisation; writing – original draft; writing – reviewing and editing
Howard Thom - Conceptualisation; formal analysis; funding acquisition; methodology; investigation; project administration; supervision of network meta-analysis and economic modelling; visualisation; writing – original draft; writing – reviewing and editing

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10.4 Data-sharing statement

All data extracted for the systematic review and the results of the risk of bias assessments are provided in full in the appendices to this report. The economic model can be obtained from the corresponding author and will be shared upon reasonable request for academic collaboration.

10.5 Ethics Statement

The MS Registry analyses worked with primary data. This was approved by the 21/SW/0085 Southwest central Bristol ethics committee. The remainder of the research included in this report is secondary research and as such did not require ethical approval.

10.6 Information Governance Statement

There were no personal data involved in the production of this report.

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322. Liu C, Blumhardt LD. Randomized, double-blind, placebo-controlled study of subcutaneous interferon beta-1a in relapsing-remitting multiple sclerosis: a categorical disability trend analysis. *Multiple Sclerosis* 2002;**8**(1): 10-14
323. Patten SB, Metz LM. Interferon beta-1 a and depression in relapsing-remitting multiple sclerosis: an analysis of depression data from the PRISMS clinical trial. *Multiple Sclerosis* 2001;**7**(4): 243-248
324. Freedman MS, Brod S, Singer BA, Cohen BA, Hayward B, Dangond F*, et al.* Clinical and MRI efficacy of sc IFN beta-1a tiw in patients with relapsing MS appearing to transition to secondary progressive MS: post hoc analyses of PRISMS and SPECTRIMS. *Journal of Neurology* 2020;**267**(1): 64-75
325. Traboulsee A, Li D, Tam R, Zhao G, Riddehough A, Fang J*, et al.* Subcutaneous interferon beta-1a three times weekly and the natural evolution of gadolinium-enhancing lesions into chronic black holes in relapsing and progressive multiple sclerosis: Analysis of PRISMS and SPECTRIMS trials. *Multiple Sclerosis Journal - Experimental, Translational and Clinical* 2017;**3**(4): 2055217317745340
326. NCT00078338. *Rebif® Versus Copaxone® in the Treatment of Relapsing Remitting Multiple Sclerosis*. URL: https://classic.clinicaltrials.gov/show/NCT00078338 (Accessed 8 May 2024).
327. Biogen Idec Research Limited. *Impact of Natalizumab versus Fingolimod on Central Nervous System (CNS) Tissue Damage and Recovery in Active Relapsing-Remitting Multiple*

Sclerosis (RRMS) Subjects.2014. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2013-004622-29 (Accessed 8 May 2024).
328. NCT02342704. *Impact of Natalizumab Versus Fingolimod in Relapsing-Remitting Multiple Sclerosis (RRMS) Participants*. URL: https://classic.clinicaltrials.gov/show/NCT02342704 (Accessed 8 May 2024).
329. NCT01440101. *Natalizumab (BG00002, Tysabri) Study in Japanese Participants With Relapsing-Remitting Multiple Sclerosis (RRMS)*. URL: https://classic.clinicaltrials.gov/show/NCT01440101 (Accessed 8 May 2024).
330. Saida T, Kira J-I, Kishida S, Yamamura T, Ohtsuka N, Dong Q*, et al.* Natalizumab for Achieving Relapse-Free, T1 Gadolinium-Enhancing-Lesion-Free, and T2 Lesion-Free Status in Japanese Multiple Sclerosis Patients: A Phase 2 Trial Subanalysis. *Neurology and Therapy* 2017;**6**(1): 153-159
331. Barkhof F, de Jong R, Sfikas N, de Vera A, Francis G, Cohen J. The influence of patient demographics, disease characteristics and treatment on brain volume loss in Trial Assessing Injectable Interferon vs FTY720 Oral in Relapsing-Remitting Multiple Sclerosis (TRANSFORMS), a phase 3 study of fingolimod in multiple sclerosis. *Multiple Sclerosis* 2014;**20**(13): 1704-1713
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334. Novartis Pharma Services. *A 12-month double-blind, randomized, multicenter, active controlled, parallel-group study comparing the efficacy and safety of 0.5 mg and 1.25 mg fingolimod (FTY720) administered orally once daily versus interferon ß-1a (Avonex®) administered i.m. once weekly in patients with relapsing-remitting multiple sclerosis with optional Extension Phase - D2302 & E1*.2006. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2006-000704-17 (Accessed 8 May 2024).
335. NCT00340834. *Efficacy and Safety of Fingolimod in Patients With Relapsing-remitting Multiple Sclerosis With Optional Extension Phase*. URL: https://classic.clinicaltrials.gov/show/NCT00340834 (Accessed 8 May 2024).
336. Duquette P, Girard M, Despault L, DuBois R, Knobler RL, Lublin FD*, et al.* Interferon beta-1b is effective in relapsing-remitting multiple sclerosis. I. Clinical results of a multicenter, randomized, double-blind, placebo- controlled trial. *Neurology* 1993;**43**(4 I): 655-661
337. Pokorski RJ. Long-term survival experience of patients with multiple sclerosis. *Journal of insurance medicine* 1997;**29**(2): 101-106
338. Manouchehrinia A, Tanasescu R, Tench CR, Constantinescu CS. Mortality in multiple sclerosis: meta-analysis of standardised mortality ratios. *Journal of neurology, neurosurgery, and psychiatry* 2016;**87**(3): 324-331
339. National Institute for Health Care Excellence (NICE). *Roflumilast for the management of severe chronic obstructive pulmonary disease*.2012. URL: http://www.nice.org.uk/guidance/ta244 (Accessed 2 May 2024).

Appendix 1
Literature search strategies
Clinical effectiveness searches

Database: Ovid (MEDALL)
Host: Ovid
Data parameters: 1946 to April 130, 2024
Date of search: 1 May 2024

#	Search terms	Results
1	Multiple Sclerosis, Relapsing-Remitting/ or ((("multiple sclerosis*" or MS) and (relap* or remit*)) or RRMS).ti,ab,kf,kw.	22740
2	Natalizumab/ or (natalizumab* or antegren* or tyruko* or tysabri* or "AN-100226*" or "AN 100226*" or AN100226* or "bg-0002" or "bg 0002" or bg0002 or "dst-356a1" or "dst 356a1" or dst356a1 or "pb-006" or "pb 006" or pb006 or "pbp-2002" or "pbp 2002" or pbp2002 or L04AA23 or 3JB47N2Q2P or "189261−10−7").ti,ab,kf,kw.	3358
3	(glatiramer* or copaxobene* or copaxone* or copemyl* or copolymer* or glatect* or galtipex* or glataxon* or glatimyl* or glatopa* or glaxaton* or marcyto* or myeloxen* or perscleran* or remurel* or sclerthon* or "tv 5010" or "tv-5010" or tv5010 or "COP 1" or "COP-1" or COP1 or "Copolymer-1" or (tv adj "5010") or u782c039qp or L03AX13 or U782C039QP or "28704-27-0" or "147245−92−9").ti,ab,kf,kw.	52890
4	*INTERFERON-BETA/ or ((INTERFERON adj2 (BETA* or fibroblast)) or avonex* or extavia* or feron* or fiblaferon* or fibrolast* or frone* or hemeferon* or naferon* or "bm 532" or "bm-532" or bm532 or "SNG 001" or "SNG-001" or SNG001 or "mr 21" or "mr-21" or mr21 or V9GU1EM8SF or "74899-71-1").ti,ab,kf,kf.	15774
5	ALEMTUZUMAB/ or (alemtuzumab* or campath* or lemtrada* or mabcambath* or mabkampat* or remniq* or "bxt 1523" or "bxt-1523" or bxt1523 or "gz 402673" or "gz-402673" or gz402673 or "ldp 03" or "ldp 103" or "ldp-103" or ldp103 or L04AA34 or 3A189DH42V or "216503-57-0").ti,ab,kf,kw.	4050
6	cladribine/ or (cladribine* or biodribin* or intocel* or leustat* or leustatin* or litak* or mavenclad* or movectro* or mylinax* or "RWJ 26251" or "RWJ-26251" or RWJ26251 or L04AA40 or 47M74X9YT5 or "4291-63-8").ti,ab,kf,kw.	2634
7	Fingolimod Hydrochloride/ or (fingolimod* or bonaxon* or chantico* or efigalo* or fenoxa* or fimodigo* or fingod* or "fty 720" or "fty-720" or fty720 or gilenia* or gilenya* or golpimec* or imusera* or inzolfi* or lognif* or "ro 7079904" or "ro-7079904" or ro7079904 or tascenso* or "tdi 132" or "tdi-132" or tdi132 or L04AA27 or 3QN8BYN5QF or "162359-55-9").ti,ab,kf,kw.	4682
8	(ocrelizumab* or ocrevus* or rhumba* or "PR 070769" or "PR-070769" or PR070769 or "R 1594" or "R-1594" or R1594 or "RG 1594" or "RG-1594" or RG1594 or "RO 4964913" or "RO-4964913" or RO4964913 or L04AA36 or A10SJL62JY or "637334-45-3").ti,ab,kf,kw.	980
9	(ofatumumab* or arzerra* or kesimpta* or "HuMax CD20" or "HuMax-CD20" or HuMaxCD20 or "humac CD20" or "humac-CD20" or humacCD20 or "GSK 1841157" or "GSK-1841157" or GSK1841157 or "HSDB 8170" or "HSDB-8170" or HSDB8170 or "OMB 157" or "OMB-157" or OMB157 or L01FA02 or M95KG522R0 or "679818-59-8").ti,ab,kf,kw.	777

#	Search terms	Results
10	(ponesimod* or ponvory* or "ACT 128800" or "ACT-128800" or ACT128800 or "r 3477" or "r-3477" or r3477 or "rg 3477" or "rg-3477" or rg3477 or L04AA50 or 5G7AKV2MKP or "854107-55-4").ti,ab,kf,kw.	122
11	HEMATOPOIETIC STEM CELL TRANSPLANTATION/ or ((haematopoietic and stem and cell and transplant*) or (haematopoietic and stem and cell and therap*) or (hematopoietic and stem and cell and transplant*) or (hematopoietic and stem and cell and therap*) or (HSC adj1 (therap* or transplant*))).ti,ab,kf,kw.	79877
12	2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11	159934
13	randomized controlled trial.pt.	612247
14	controlled clinical trial.pt.	95537
15	random*.ti,ab,kf,kw.	1517590
16	placebo.ab.	247945
17	("Phase 3*" or "phase3*" or "phase III*" or P3* or "PIII*" or "Phase 2*" or "phase2*" or "phase II*" or P2* or "PII*").ti,ab,kw,kf.	407300
18	(trial or trail).ti,ab,kw,kf.	835874
19	13 or 14 or 15 or 16 or 17 or 18	2430396
20	1 and 12 and 19	2022

Database: Embase
Host: Ovid
Data parameters: 1974 to 2024 April 30
Date of search: 1 May 2024

#	Search terms	Results
1	*relapsing remitting multiple sclerosis/ or ((("multiple sclerosis*" or MS) and (relap* or remit*)) or RRMS).ti,ab,kf,kw.	45210
2	natalizumab/ or (natalizumab* or antegren* or tyruko* or tysabri* or "AN-100226*" or "AN 100226*" or AN100226* or "bg-0002" or "bg 0002" or bg0002 or "dst-356a1" or "dst 356a1" or dst356a1 or "pb-006" or "pb 006" or pb006 or "pbp-2002" or "pbp 2002" or pbp2002 or L04AA23 or 3JB47N2Q2P or "189261−10−7").ti,ab,kf,kw.	14696
3	*glatiramer/ or (glatiramer* or copaxobene* or copaxone* or copemyl* or copolymer* or glatect* or galtipex* or glataxon* or glatimyl* or glatopa* or glaxaton* or marcyto* or myeloxen* or perscleran* or remurel* or sclerthon* or "tv 5010" or "tv-5010" or tv5010 or "COP 1" or "COP-1" or COP1 or "Copolymer-1" or (tv adj "5010") or u782c039qp or L03AX13 or U782C039QP or "28704-27-0" or "147245−92−9").ti,ab,kf,kw.	55546
4	*beta interferon/ or ((INTERFERON adj2 (BETA* or fibroblast)) or avonex* or extavia* or feron* or fiblaferon* or fibrolast* or frone* or hemeferon* or naferon* or "bm 532" or "bm-532" or bm532 or "SNG 001" or "SNG-001" or SNG001 or "mr 21" or "mr-21" or mr21 or V9GU1EM8SF or "74899-71-1").ti,ab,kf,kf.	23719
5	*alemtuzumab/ or (alemtuzumab* or campath* or lemtrada* or mabcambath* or mabkampat* or remniq* or "bxt 1523" or "bxt-1523" or bxt1523 or "gz 402673" or "gz-402673" or gz402673 or "ldp 03" or "ldp 103" or "ldp-103" or ldp103 or L04AA34 or 3A189DH42V or "216503-57-0").ti,ab,kf,kw.	9493
6	*cladribine/ or (cladribine* or biodribin* or intocel* or leustat* or leustatin* or litak* or mavenclad* or movectro* or mylinax* or "RWJ 26251" or "RWJ-26251" or RWJ26251 or L04AA40 or 47M74X9YT5 or "4291-63-8").ti,ab,kf,kw.	4644

#	Search terms	Results
7	*fingolimod/ or (fingolimod* or bonaxon* or chantico* or efigalo* or fenoxa* or fimodigo* or fingod* or "fty 720" or "fty-720" or fty720 or gilenia* or gilenya* or golpimec* or imusera* or inzolfi* or lognif* or "ro 7079904" or "ro-7079904" or ro7079904 or tascenso* or "tdi 132" or "tdi-132" or tdi132 or L04AA27 or 3QN8BYN5QF or "162359-55-9").ti,ab,kf,kw	9012
8	*ocrelizumab/ or (ocrelizumab* or ocrevus* or rhumba* or "PR 070769" or "PR-070769" or PR070769 or "R 1594" or "R-1594" or R1594 or "RG 1594" or "RG-1594" or RG1594 or "RO 4964913" or "RO-4964913" or RO4964913 or L04AA36 or A10SJL62JY or "637334-45-3").ti,ab,kf,kw.	2587
9	*ofatumumab/ or (ofatumumab* or arzerra* or kesimpta* or "HuMax CD20" or "HuMax-CD20" or HuMaxCD20 or "humac CD20" or "humac-CD20" or humacCD20 or "GSK 1841157" or "GSK-1841157" or GSK1841157 or "HSDB 8170" or "HSDB-8170" or HSDB8170 or "OMB 157" or "OMB-157" or OMB157 or L01FA02 or M95KG522R0 or "679818-59-8").ti,ab,kf,kw.	1932
10	*ponesimod/ or (ponesimod* or ponvory* or "ACT 128800" or "ACT-128800" or ACT128800 or "r 3477" or "r-3477" or r3477 or "rg 3477" or "rg-3477" or rg3477 or L04AA50 or 5G7AKV2MKP or "854107-55-4").ti,ab,kf,kw.	257
11	*autologous hematopoietic stem cell transplantation/ or ((haematopoietic and stem and cell and transplant*) or (haematopoietic and stem and cell and therap*) or (hematopoietic and stem and cell and transplant*) or (hematopoietic and stem and cell and therap*) or (HSC adj1 (therap* or transplant*))).ti,ab,kf,kw.	983369
12	2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11	206490
13	randomized controlled trial/	818976
14	controlled clinical trial/	473299
15	random*.ti,ab,kf,kw.	2068701
16	placebo.ab.	366592
17	("Phase 3*" or "phase3*" or "phase III*" or P3* or "PIII*" or "Phase 2*" or "phase2*" or "phase II*" or P2* or "PII*").ti,ab,kw,kf.	638979
18	(trial or trail).ti,ab,kw,kf.	1218800
19	13 or 14 or 15 or 16 or 17 or 18	5332
20	1 and 12 and 19	2194

Clinical Trials.gov
Date of search: 8 May 2024
URL: https://classic.clinicaltrials.gov/ct2/results/refine?show_xprt=Y
Searcher location: London, UK

344 Studies found for: (Relapsing AND Remitting AND multiple sclerosis OR RRMS) AND ((natalizumab OR Tysabri OR antegren OR tyruko) OR (glatiramer OR copaxone OR brabio OR glatopa OR copolymer) OR (INTERFERON-BETA OR IFN-beta) OR (alemtuzumab OR campath OR lemtrada) OR (cladribine OR leustatin OR mavenclad) OR (fingolimod OR gilenya) OR (ocrelizumab OR ocrevus) AND OR AND (ofatumumab ORarzerra OR kesimpta OR HuMax-CD20) OR (ponesimod OR ponvory) OR autologous AND haematopoietic AND stem AND cell AND transplantation)

WHO ICTRP
Date of search: 8 May 2024
URL: https://trialsearch.who.int/Default.aspx
Searcher location: London, UK

(((Relapsing AND Remitting AND multiple sclerosis) OR (RRMS)) AND ((natalizumab OR Tysabri OR antegren OR tyruko) OR (glatiramer OR copaxone OR brabio OR glatopa OR copolymer) OR (INTERFERON-BETA OR IFN-beta) OR (alemtuzumab OR campath OR lemtrada) OR (cladribine OR leustatin OR mavenclad) OR (fingolimod OR gilenya) OR (ocrelizumab OR ocrevus) OR (ofatumumab ORarzerra OR kesimpta OR HuMax-CD20) OR (ponesimod OR ponvory) OR (autologous AND haematopoietic AND stem AND cell AND transplantation)))

Cost effectiveness and economics searches

Database: Ovid (MEDALL)
Host: Ovid
Data parameters: 1946 to May 14, 2024
Date of search: 15 May 2024

#	Search terms	Results
1	Multiple Sclerosis, Relapsing-Remitting/ or *Multiple Sclerosis, Chronic Progressive/ or (RRMS or RMS or SPMS or (("multiple sclerosis*" or MS) adj5 (relap* or remit* or secondary or progres*))).ti,ab,kf,kw.	44865
2	exp "Costs and Cost Analysis"/	270448
3	exp Economics, Hospital/ or Financial management, hospital/	33116
4	Economics, Medical/	9280
5	economics, nursing/	4013
6	economics, pharmaceutical/	3134
7	(economic* or cost or costs or costly or costing or expense or expenses or financial or price or prices or pricing or pharmacoeconomic* or "pharmaco-economic*" or CEA or CUA or CBA or CMA).ti,ab,kf,kw.	1293465
8	exp "fees and charges"/	31446
9	exp budgets/	14209
10	(resource*1 and (allocation or utili* or usage or use*1)).ti,ab,kf,kw.	289137
11	(expenditure* not energy).ti,ab,kw.	38946
12	(value adj1 (money or monetary)).ti,ab,kw.	922
13	(budget* or fiscal or funding or financial or finance*).ti,ab,kw.	252168
14	("decision tree" or Markov or "semi Markov" or "partitioned adj2 survival" or "discrete event" or "conceptual* adj2 model*" or (decision adj2 model*) or "outcome model*" or "causal model*" or (simulat* adj2 model*) or "monte carlo" or "decision tree" or QALY*).ti,ab,kf.	170283
15	2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14	1864162
16	1 and 15	2164
17	(2014* or 2015* or 2016* or 2017* or 2018* or 2019* or 2020* or 2021* or 2022* or 2023* or 2024*).dt,dp,ed,ep,yr.	14514910
18	16 and 17	1492

Database: Embase
Host: Ovid
Data parameters: 1974 to 2024 May 14
Date of search: 15 May 2024

#	Search terms	Results
1	*relapsing remitting multiple sclerosis/ or *progressive multiple sclerosis/ or (RRMS or RMS or SPMS or (("multiple sclerosis*" or MS) adj5 (relap* or remit* or secondary or progres*))).ti,ab,kf,kw.	68614
2	health-economics/	36483
3	exp economic-evaluation/	367967
4	exp health-care-cost/	352578
5	exp pharmacoeconomics/	241926
6	economics, pharmaceutical/	3134
7	(economic* or cost or costs or costly or costing or expense or expenses or financial or price or prices or pricing or pharmacoeconomic* or "pharmaco-economic*" or CEA or CUA or CBA or CMA).ti,ab,kf,kw.	1658860
8	(resource*1 and (allocation or utili* or usage or use*1)).ti,ab,kf,kw.	380346
9	(expenditure* not energy).ti,ab,kw.	52598
10	(value adj1 (money or monetary)).ti,ab,kw.	3114
11	(budget* or fiscal or funding or financial or finance*).ti,ab,kw.	372153
12	("decision tree" or Markov or "semi Markov" or "partitioned adj2 survival" or "discrete event" or "conceptual* adj2 model*" or (decision adj2 model*) or "outcome model*" or "causal model*" or (simulat* adj2 model*) or "monte carlo" or "decision tree" or QALY*).ti,ab,kf.	206543
13	2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14	2592681
14	(2014* or 2015* or 2016* or 2017* or 2018* or 2019* or 2020* or 2021* or 2022* or 2023* or 2024*).yr.	17479900
15	1 and 12 and 13	2907
16	limit 14 to embase	1229

Database: Econlit
Host: EBSCOhost
Data parameters: 1981-current
Date of search: 15 May 2024

#	Search terms	Results
1	AB (("RRMS" or "SPMS" or (("multiple sclerosis*" or MS) N5 (relap* or remit* or secondary or progres*)))) OR TI (("RRMS" or "SPMS" or (("multiple sclerosis*" or MS) N5 (relap* or remit* or secondary or progres*))))	17

Database: NHS EED (via CRD Databases)
Host: https://www.crd.york.ac.uk/CRDWeb/HomePage.asp
Data parameters: unreported
Date of search: 15 May 2024

#	Search terms	Results
1	AB (("RRMS" or "SPMS" or (("multiple sclerosis*" or MS) AND (relap* or remit* or secondary or progres*)))) OR TI (("RRMS" or "SPMS" or (("multiple sclerosis*" or MS) N5 (relap* or remit* or secondary or progres*))))	6

Appendix 2
Tables of ongoing, or excluded studies

On-going studies

Table 38 On-going studies that appear to meet inclusion criteria

Citation	Interventions of interest for this appraisal
Brittain G, Petrie J, Duffy K, et al. Efficacy and safety of autologous haematopoietic stem cell transplantation versus alemtuzumab, ocrelizumab, ofatumumab or cladribine in relapsing remitting multiple sclerosis (StarMS): protocol for a randomised controlled trial. BMJ open. 2024;14(2):e083582. doi:10.1136/bmjopen-2023-083582.	Autologous haematopoietic stem cell transplantation versus alemtuzumab, ocrelizumab, ofatumumab or cladribine
NCT03477500. *Randomized Autologous Hematopoetic Stem Cell Transplantation Versus Alemtuzumab, Cladribine or Ocrelizumab for RRMS (RAM-MS)*. URL: https://classic.clinicaltrials.gov/show/NCT03477500 (Accessed 8 May 2024).	
NCT05906992. *A Study to Compare Efficacy, Pharmacokinetics, Pharmacodynamics and Safety of CT-P53 and Ocrevus in Patients With Relapsing-remitting Multiple Sclerosis*.2023. URL: https://clinicaltrials.gov/show/NCT05906992 (Accessed 8 May 2024).	Ocrelizumab
NCT04047628. *Best Available Therapy Versus Autologous Hematopoetic Stem Cell Transplant for Multiple Sclerosis (BEAT-MS)*. URL: https://classic.clinicaltrials.gov/show/NCT04047628 (Accessed 8 May 2024).	Autologous Hematopoetic Stem Cell Transplantation
NCT04788615. *Open Label Randomized Multicenter to Assess Efficacy & Tolerability of Ofatumumab 20mg vs. First Line DMT in RMS*. URL: https://classic.clinicaltrials.gov/show/NCT04788615 (Accessed 8 May 2024).	Ofatumumab
NCT00176592. *Phase IV Study, Betaseron Versus Copaxone for Relapsing Remitting or CIS Forms of MS Using Triple Dose Gad 3 T MRI*. URL: https://classic.clinicaltrials.gov/show/NCT00176592 (Accessed 8 May 2024).	interferon beta-1b and glatiramer acetate
NCT01058005. *Study Evaluating Rebif, Copaxone, and Tysabri for Active Multiple Sclerosis*. URL: https://classic.clinicaltrials.gov/show/NCT01058005 (Accessed 8 May 2024).	interferon beta-1a and glatiramer acetate and Natilziumab
2019-001549-42. *Stem cell transplantation versus disease modifying therapy (alemtuzumab or ocrelizumab) for patients with highly active relapsing remitting MS*.2020. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2019-001549-42 (Accessed 8 May 2024).	Stem cell transplantation versus disease modifying therapy (alemtuzumab or ocrelizumab)
2010-023560-40. *Blood stem cell transplantation for patients with relapsing-remitting multiple sclerosis, in whom standard treatment has failed*.2010. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2010-023560-40 (Accessed 8 May 2024).	Stem cell transplantation versus disease modifying therapy (alemtuzumab or ocrelizumab)

Studies included in manufacturers' submissions

Below we tabulate decisions made and reasons for exclusion, where applicable, for studies reported in submissions from manfuacturers.

Table 39 Studies included in submission from BIOGEN

Study Name	Reference	Decision
AFFIRM	Polman CH, O'Connor PW, Havrdova E, *et al.* A Randomized, Placebo-Controlled Trial of Natalizumab for Relapsing Multiple Sclerosis. *N Engl J Med*. 2006;354(9):899–910. https://doi.org/10.1056/NEJMoa044397.	Included
	Hutchinson M, Kappos L, Calabresi PA, *et al.* The efficacy of natalizumab in patients with relapsing multiple sclerosis: subgroup analyses of AFFIRM and SENTINEL. *J Neurol*. 2009;256(3):405–415. https://doi.org/10.1007/s00415-009-0093-1.	Included
DELIVER	Plavina T, Fox EJ, Lucas N, Muralidharan KK, Mikol D. A Randomized Trial Evaluating Various Administration Routes of Natalizumab in Multiple Sclerosis. *J Clin Pharmacol*. 2016;56(10):1254–1262. https://doi.org/10.1002/jcph.707.	Excluded - Comparison of different administration routes
NOVA	Foley JF, Defer G, Ryerson LZ, *et al.* Comparison of switching to 6-week dosing of natalizumab versus continuing with 4-week dosing in patients with relapsing-remitting multiple sclerosis (NOVA): a randomised, controlled, open-label, phase 3b trial. *Lancet Neurol*. 2022;21(7):608–619. https://doi.org/10.1016/S1474-4422(22)00143-0.	Excluded - Comparison of different dosing schedules
REFINE	Trojano M, Ramió-Torrentà L, Grimaldi LM, *et al.* A randomized study of natalizumab dosing regimens for relapsing-remitting multiple sclerosis. *Mult Scler Houndmills Basingstoke Engl*. 2021;27(14):2240–2253.	Excluded - Comparison of different doses
TOP	Trojano M, Wiendl H, Kappos L, *et al.* TYSABRI Observational Program: Long-term Safety and Effectiveness in Relapsing-Remitting Multiple Sclerosis over 15 Years. EPO-658. Presented at European Academy of Neurology 9th Congress, 1-4 July. 2023.	Excluded - Observational Study
	Nicholas R, Harrower T, Sun Z, Davies H. Long-term Effectiveness of Natalizumab for RRMS: UK and Global 2022 Results from TYSABRI Observational Program. P184. Presented at Association of British Neurologists. 9-12 May. 2023.	

Table 40 Studies included in submission from Sandoz

Study name	Study Details	Decision
AFFIRM	Polman CH, O'Connor PW, Havrdova E, et al. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. N Engl J Med 2006;354:899-910.	Included
ANTELOPE	Hemmer B, Wiendl H, Roth K, et al. Efficacy and Safety of Proposed Biosimilar Natalizumab (PB006) in Patients With Relapsing-Remitting Multiple Sclerosis: The Antelope Phase 3 Randomized Clinical Trial. JAMA Neurol 2023;80:298-307.	Included
DELIVER	Plavina T, Fox EJ, Lucas N, et al. A Randomized Trial Evaluating Various Administration Routes of Natalizumab in Multiple Sclerosis. J Clin Pharmacol 2016;56:1254-62.	Excluded – not informative to the network: compares different protocols [Report excluded in Nested but no reason was given]
NEXT-MS	Toorop AA, van Kempen ZLE, Steenhuis M, et al. Decrease of natalizumab drug levels after switching from intravenous to subcutaneous administration in patients with multiple sclerosis. J Neurol Neurosurg Psychiatry 2023;94:482-486.	Excluded – not an RCT
REFINE	Trojano M, Ramió-Torrentà L, Grimaldi LM, et al. A randomized study of natalizumab dosing regimens for relapsing-remitting multiple sclerosis. Mult Scler 2021;27:2240-2253.	Excluded - Comparison of different doses
	ClinicalTrials.gov. Exploratory Study of the Safety, Tolerability and Efficacy of Multiple Regimens of Natalizumab in Adult Participants With Relapsing Multiple Sclerosis (MS) (REFINE). Available from: https://classic.clinicaltrials.gov/ct2/show/NCT01405820. [Last Accessed: 13th February 2024].	
TOP	Butzkueven H, Kappos L, Wiendl H, et al. Long-term safety and effectiveness of natalizumab treatment in clinical practice: 10 years of real-world data from the Tysabri Observational Program (TOP). Journal of Neurology, Neurosurgery & Psychiatry 2020;91:660-668.	Excluded - Observational Study
	Butzkueven H, Kappos L, Spelman T, et al. No evidence for loss of natalizumab effectiveness with every-6-week dosing: a propensity score-matched comparison with every-4-week dosing in patients enrolled in the Tysabri Observational Program (TOP). Ther Adv Neurol Disord 2021;14:17562864211042458.	
NR	Samjoo IA, Drudge C, Walsh S, et al. Comparative efficacy of therapies for relapsing multiple sclerosis: a systematic review and network meta-analysis. J Comp Eff Res 2023;12:e230016.	Excluded – Review (references screened)
NR	Filippi M, Danesi R, Derfuss T, et al. Early and unrestricted access to high-efficacy disease-modifying therapies: a consensus to optimize benefits for people living with multiple sclerosis. J Neurol 2022;269:1670-1677.	Excluded – Commentary
NR	Pfeuffer S, Ruck T, Pul R, et al. Impact of previous disease-modifying treatment on effectiveness and safety outcomes, among patients with multiple sclerosis treated with alemtuzumab. J Neurol Neurosurg Psychiatry 2021;92:1007-1013.	Excluded - Observational Study

Study name	Study Details	Decision
NR	Killestein J, van Oosten B. Emerging safety issues in alemtuzumab-treated MS patients. Multiple Sclerosis Journal 2019;25:1206-1208.	Excluded - Editorial
NR	ClinicalTrials.gov. Safety Study of Natalizumab to Treat Multiple Sclerosis (MS). Available from: https://classic.clinicaltrials.gov/ct2/show/NCT00559702. [Last Accessed: 13th February 2024].	Excluded – Not informative to the network – compares different protocols
NR	ClinicalTrials.gov. A Study to Evaluate Efficacy, Safety, Pharmacokinetics, and Pharmacodynamics of Multiple Doses of Natalizumab (BG00002) Administered Subcutaneously to Japanese Participants With Relapsing-Remitting Multiple Sclerosis. Available from: https://classic.clinicaltrials.gov/ct2/show/NCT05265728. [Last Accessed: 12th February 2024].	Excluded – Not an RCT
NR	ClinicalTrials.gov. A Study to Investigate the Radiological Onset of Action After Treatment Initiation With Subcutaneous (SC) Natalizumab in Participants With Relapsing-Remitting Multiple Sclerosis (RRMS). Available from: https://classic.clinicaltrials.gov/ct2/show/NCT05532163. [Last Accessed: 12th Februrary 2024].	Excluded – Not an RCT (& terminated)
NR	Gelissen LMY, Loveless S, Toorop AA, et al. Subcutaneous administration of natalizumab can lead to lower drug concentrations compared to intravenous administration. Mult Scler Relat Disord 2024;90:105796.	Excluded – Not an RCT
NR	Pelle J, Briant AR, Branger P, et al. Real-World Effectiveness of Natalizumab Extended Interval Dosing in a French Cohort. Neurol Ther 2023;12:529-542.	Excluded – Observational study
NR	Perncezky J, Sellner J. Natalizumab extended-interval dosing in multiple sclerosis to mitigate progressive multifocal leukoencephalopathy risk: initial study evidence and real-world experience. J Cent Nerv Syst Dis 2022;14:11795735221135485.	Excluded – Review
NR	Achtnichts L, Zecca C, Findling O, et al. Correlation of disability with quality of life in patients with multiple sclerosis treated with natalizumab: primary results and post hoc analysis of the TYSabri ImPROvement study (PROTYS). BMJ Neurol Open. 2023;5(1):e000304.	Excluded – Observational study

Studies excluded at full-text screening

Table 41 Reports excluded at full-text screening

Citation	Reason for exclusion
Abbasi Kasbi N, Ghadiri F, Sahraian M, et al. Comparing infusion-related reactions of the first full dose (600 mg) biosimilar ocrelizumab administration with the standard divided protocol in multiple sclerosis patients: a randomized controlled trial study. Acta neurologica Belgica. 2024;124(1):205-212. doi:10.1007/s13760-023-02366-z.	MS but not >90% RRMS
Abdar M, Ebrahimifar P, Etemadifar M. The outbreak fingolimod cardiovascular side effects in relapsing-remitting multiple sclerosis patient: A longitudinal study in an Iranian population. ARYA atherosclerosis. 2016;12(6):274-280.	Does not report on one of the outcomes of interest
Abdelgaied M, Rashad M, El-Tayebi H, Solayman M. Correction to: The impact of metformin use on the outcomes of relapse-remitting multiple sclerosis patients receiving interferon beta 1a: an exploratory prospective phase II open-label randomized controlled trial. Journal of neurology. 2024;271(5):2925. doi:10.1007/s00415-024-12249-9.	Not informative to the network - non DMT add on
Abdelgaied M, Rashad M, El-Tayebi H, Solayman M. The impact of metformin use on the outcomes of relapse-remitting multiple sclerosis patients receiving interferon beta 1a: an exploratory prospective phase II open-label randomized controlled trial. Journal of neurology. 2024;271(3):1124-1132. doi:10.1007/s00415-023-12113-2.	Not informative to the network - non DMT add on
Abramowicz M. Glatiramer acetate for relapsing multiple sclerosis. Medical Letter on Drugs and Therapeutics. 1997;39(1004):61-64.	Not a primary study
Irct2013020812398N. *The Effectiveness, Safety and Tolerability of Actovex® Compared to Avonex® in Subjects with Relapsing Remitting Multiple Sclerosis (RRMS)*.2014. URL: http://en.irct.ir/trial/12461 (Accessed 8 May 2024).	Not informative to the network - compares brands
Aivo J, Lindsrom B, Soilu-Hanninen M. A Randomised, Double-Blind, Placebo-Controlled Trial with Vitamin D3 in MS: Subgroup Analysis of Patients with Baseline Disease Activity Despite Interferon Treatment. Multiple sclerosis international. 2012;2012:802796. doi:10.1155/2012/802796.	Not informative to the network - non DMT add on
Albert C, Mikolajczak J, Liekfeld A, et al. Fingolimod after a first unilateral episode of acute optic neuritis (MOVING) - preliminary results from a randomized, rater-blind, active-controlled, phase 2 trial. BMC neurology. 2020;20(1):75. doi:10.1186/s12883-020-01645-z.	MS but not >90% RRMS
Irct20170128032241N. *Effect of oral curcuden on multiple sclerosis patients*.2018. URL: http://en.irct.ir/trial/25165 (Accessed 8 May 2024).	Did not evaluate intervention of interest
ACTRN12619000348156. *Autologous Haematopoietic Stem Cell Transplantation for highly active treatment resistant multiple sclerosis*.2019. URL: https://anzctr.org.au/ACTRN12619000348156.aspx (Accessed 8 May 2024).	Not an RCT
jRCT2051210146. *Phase 3 Study to Evaluate Efficacy, Safety, PK, and PD of SC Natalizumab in Japanese Participants With RRMS*.2021. URL: https://jrct.niph.go.jp/latest-detail/jRCT2051210146 (Accessed 8 May 2024).	Not an RCT

Citation	Reason for exclusion
NCT05296161. B Cell Tailored Ocrelizumab Versus Standard Ocrelizumab in Relapsing Remitting Multiple Sclerosis.2022. URL: https://clinicaltrials.gov/show/NCT05296161 (Accessed 8 May 2024).	Not informative to the network - DMT add on
Anderson G, Meyer D, Herrman C, et al. Tolerability and safety of novel half milliliter formulation of glatiramer acetate for subcutaneous injection: an open-label, multicenter, randomized comparative study. Journal of neurology. 2010;257(11):1917-23. doi:10.1007/s00415-010-5779-x.	Not informative to the network - compares different protocols
Anonymous. Alemtuzumab (Campath) off-label for relapsing multiple sclerosis. Medical Letter on Drugs and Therapeutics. 2009;51(1307):17-18.	Not a primary study
Anonymous. Avonex 30 mug i.m. once a week is the correct dose for the therapy of relapsing-remitting multiple sclerosis. Deutsche Apotheker Zeitung. 2000;140(50):38.	Not a primary study
Anonymous. Erratum to Daclizumab in active relapsing multiple sclerosis (CHOICE study): A phase 2, randomised, double-blind, placebo-controlled, add-on trial with interferon beta [Lancet Neurol, (2010), 9, 381-90]. The Lancet Neurology. 2010;9(8):759. doi:10.1016/s1474-4422(10)70172-1.	Not informative to the network - non DMT add on
Anonymous. Erratum to Methylprednisolone in combination with interferon beta-1a for relapsing-remitting multiple sclerosis (MECOMBIN study): A multicentre, double-blind, randomised, placebo controlled, parallel-group trial [Lancet Neurol, (2010), 9, 672-80]. The Lancet Neurology. 2010;9(8):759. doi:10.1016/s1474-4422(10)70171-x.	Not informative to the network - non DMT add on
Anonymous. Evidence of interferon beta-1a dose response in relapsing-remitting MS: the OWIMS Study. The Once Weekly Interferon for MS Study Group. Neurology. 1999;53(4):679-86. doi:10.1212/wnl.53.4.679.	Did not evaluate intervention of interest - drug is of interest but in different presentation/dose than licensed
Anonymous. Glatiramer acetate for multiple sclerosis. Drug and Therapeutics Bulletin. 2001;39(6):41-43. doi:10.1136/dtb.2001.39641.	Not a primary study
Anonymous. Placebo-controlled multicentre randomised trial of interferon beta-1b in treatment of secondary progressive multiple sclerosis. European Study Group on interferon beta-1b in secondary progressive MS. Lancet (London, England). 1998;352(9139):1491-7.	MS but not >90% RRMS
Anonymous. PRISMS-4: Long-term efficacy of interferon-beta-1a in relapsing MS. Neurology. 2001;56(12):1628-36. doi:10.1212/wnl.56.12.1628.	Extension/expansion study
Anonymous. Promising outcomes from Phase III CLARITY study for the treatment of multiple sclerosis announced. Expert review of pharmacoeconomics & outcomes research. 2009;9(3):198. doi:10.1586/erp.09.25.	Not a primary study
Anonymous. Randomized controlled trial of interferon- beta-1a in secondary progressive MS: Clinical results. Neurology. 2001;56(11):1496-504. doi:10.1212/wnl.56.11.1496.	MS but not >90% RRMS

Citation	Reason for exclusion
Arnold D, Calabresi P, Kieseier B, et al. Peginterferon beta-1a improves MRI measures and increases the proportion of patients with no evidence of disease activity in relapsing-remitting multiple sclerosis: 2-year results from the ADVANCE randomized controlled trial. BMC neurology. 2017;17(1):29. doi:10.1186/s12883-017-0799-0.	Extension/expansion study
Arnold D, Campagnolo D, Panitch H, et al. Glatiramer acetate after mitoxantrone induction improves MRI markers of lesion volume and permanent tissue injury in MS. Journal of neurology. 2008;255(10):1473-8. doi:10.1007/s00415-008-0911-x.	Not informative to the network - non DMT add on
Arnold D, Narayanan S, Antel S. Neuroprotection with glatiramer acetate: evidence from the PreCISe trial. Journal of neurology. 2013;260(7):1901-6. doi:10.1007/s00415-013-6903-5.	MS but not >90% RRMS
Ashtari F, Savoj M. Effects of low dose methotrexate on relapsing-remitting multiple sclerosis in comparison to Interferon beta-1alpha: A randomized controlled trial. Journal of research in medical sciences : the official journal of Isfahan University of Medical Sciences. 2011;16(4):457-62.	Not informative to the network - non DMT add on
Ashtari F, Toghianifar N, Zarkesh-Esfahani S, Mansourian M. High dose Vitamin D intake and quality of life in relapsing-remitting multiple sclerosis: a randomized, double-blind, placebo-controlled clinical trial. Neurological research. 2016;38(10):888-92. doi:10.1080/01616412.2016.1227913.	Not informative to the network - non DMT add on
Atkins H, Bowman M, Allan D, et al. Immunoablation and autologous haemopoietic stem-cell transplantation for aggressive multiple sclerosis: a multicentre single-group phase 2 trial. Lancet (London, England). 2016;388(10044):576-85. doi:10.1016/s0140-6736(16)30169-6.	Not an RCT
ACTRN12616000151437. *A Phase II study:
Haematopoietic Stem Cell Transplantation for highly active
treatment resistant multiple sclerosis .
*.2016. URL: https://anzctr.org.au/ACTRN12616000151437.aspx (Accessed 8 May 2024).	Not an RCT
Bandari D, Wynn D, Miller T, et al. Rebif(R) Quality of Life (RebiQoL): A randomized, multicenter, Phase IIIb study evaluating quality-of-life measures in patients receiving the serum-free formulation of subcutaneous interferon beta-1a for the treatment of relapsing forms of multiple sclerosis. Multiple sclerosis and related disorders. 2013;2(1):45-56. doi:10.1016/j.msard.2012.07.005.	Not informative to the network - compares different protocols
Barbero P, Verdun E, Bergui M, et al. High-dose, frequently administered interferon beta therapy for relapsing-remitting multiple sclerosis must be maintained over the long term: the interferon beta dose-reduction study. Journal of the neurological sciences. 2004;222(1-2):13-9. doi:10.1016/j.jns.2004.03.023.	Not informative to the network - compares different protocols
Bar-Or A, Grove R, Austin D, et al. Subcutaneous ofatumumab in patients with relapsing-remitting multiple sclerosis: The MIRROR study. Neurology. 2018;90(20):e1805-e1814. doi:10.1212/wnl.0000000000005516.	Did not evaluate intervention of interest - drug is of interest but in different presentation/dose than licensed
Bar-Or A, Wiendl H, Montalban X, et al. Rapid and sustained B-cell depletion with subcutaneous ofatumumab in relapsing multiple sclerosis: APLIOS, a randomized phase-2 study. Multiple sclerosis (Houndmills, Basingstoke, England). 2022;28(6):910-924. doi:10.1177/13524585211044479.	Not informative to the network - compares different protocols

Citation	Reason for exclusion
Barroso-Rodriguez N, Nunez-Orozco L, Santos-Caballero N, et al. Comparative study with random assignment and blind assessor to determine the effect on the soluble Vascular Cell Adhesion Molecules (sVCAM-1) of the Interferon Beta 1a biogeneric of Mexican production against an Interferon Beta 1a of international production in patients with Relapsing-Remitting Multiple Sclerosis (RRMS). Revista Mexicana de Neurociencia. 2008;9(4):268-272.	Not informative to the network - compares brands
Bartosik-Psujek H, Mitosek-Szewczyk K, Belniak E, Stelmasiak Z. [Development of binding antibodies to interferon-beta during treatment of multiple sclerosis with different types of interferon-beta]. Powstawanie przeciwcial wiazacych interferon beta w trakcie leczenia stwardnienia rozsianego roznymi preparatami interferonu beta. 2004;17(97):28-32.	Not an RCT
Bates D, Bartholome E. Treatment effect of natalizumab on relapse outcomes in multiple sclerosis patients despite ongoing MRI activity. Journal of neurology, neurosurgery, and psychiatry. 2012;83(1):55-60. doi:10.1136/jnnp-2011-300279.	Not an RCT
Baum K. Safety and tolerability of a 'refrigeration-free' formulation of interferon beta-1b--results of a double-blind, multicentre, comparative study in patients with relapsing-remitting or secondary progressive multiple sclerosis. The Journal of international medical research. 2006;34(1):1-12. doi:10.1177/147323000603400101.	MS but not >90% RRMS
Bell Gorrod H, Latimer N, Damian D, Hettle R, Harty G, Wong S. Assessing the Long-Term Effectiveness of Cladribine vs. Placebo in the Relapsing-Remitting Multiple Sclerosis CLARITY Randomized Controlled Trial and CLARITY Extension Using Treatment Switching Adjustment Methods. Advances in therapy. 2020;37(1):225-239. doi:10.1007/s12325-019-01140-z.	Not a primary study
Bellmann-Strobl J, Paul F, Wuerfel J, et al. Epigallocatechin Gallate in Relapsing-Remitting Multiple Sclerosis: A Randomized, Placebo-Controlled Trial. Neurology(R) neuroimmunology & neuroinflammation. 2021;8(3). doi:10.1212/nxi.0000000000000981.	Not informative to the network - non DMT add on
Benedict R, Cohan S, Lynch S, et al. Improved cognitive outcomes in patients with relapsing-remitting multiple sclerosis treated with daclizumab beta: Results from the DECIDE study. Multiple sclerosis (Houndmills, Basingstoke, England). 2018;24(6):795-804. doi:10.1177/1352458517707345.	Comparator not informative to the network
Berkovich R, Bakshi R, Amezcua L, et al. Adrenocorticotropic hormone versus methylprednisolone added to interferon beta in patients with multiple sclerosis experiencing breakthrough disease: a randomized, rater-blinded trial. Therapeutic advances in neurological disorders. 2017;10(1):3-17. doi:10.1177/1756285616670060.	Did not evaluate intervention of interest
Bermel R, Weinstock-Guttman B, Bourdette D, Foulds P, You X, Rudick R. Intramuscular interferon beta-1a therapy in patients with relapsing-remitting multiple sclerosis: a 15-year follow-up study. Multiple sclerosis (Houndmills, Basingstoke, England). 2010;16(5):588-96. doi:10.1177/1352458509360549.	Extension/expansion study
Biernacki T, Bencsik K, Sandi D, Vecsei L. [Alemtuzumab therapy 2017]. Alemtuzumabterapia, 2017. 2017;70(11-12):371-380. doi:10.18071/isz.70.0371.	Not a primary study
2005-003930-16. *A Multi-centre, Double Blind, Randomised, Placebo Controlled, Parallel Group Study Investigating Simvastatin as an Add-on Treatment to Interferon-beta-1a for the Treatment of Relapsing-Remitting Multiple Sclerosis - SIMCOMBIN*.2005. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2005-003930-16 (Accessed 8 May 2024).	Not informative to the network - non DMT add on

Citation	Reason for exclusion
2010-024000-10. A Study to Evaluate the Effect of Different Doses of TYSABRI on Safety and Efficacy in Relapsing Multiple Sclerosis.2011. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2010-024000-10 (Accessed 8 May 2024).	Not informative to the network - compares different protocols
2009-012500-11. Comparison of Daclizumab HYP and Avonex® in Multiple Sclerosis.2010. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2009-012500-11 (Accessed 8 May 2024).	Comparator not informative to the network
Ctri 380. A clinical trial to determine the efficacy and safety of BG00012 in patients with relapsing remitting multiple sclerosis.2009. URL: http://www.ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=380 (Accessed 8 May 2024).	Can't locate
ISRCTN68218781. A Multi-center, Double Blind, Randomized, Placebo Controlled, Parallel Group Trial Investigating Methylprednisolone in Combination with Interferon-beta-1a for the Treatment of Relapsing-Remitting Multiple Sclerosis.2004. URL: http://isrctn.com/ISRCTN68218781 (Accessed 8 May 2024).	Not informative to the network - non DMT add on
2018-003008-38. A Study to Evaluate the Safety, Tolerability, and Efficacy of BIIB017 (Peginterferon beta-1a) in Paediatric Participants for the Treatment of Relapsing-Remitting Multiple Sclerosis.2019. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2018-003008-38 (Accessed 8 May 2024).	RRMS but not in adults
2018-000516-22. Study to Evaluate the Efficacy and Safety of BG00012 and BIIB017 for the Treatment of Relapsing-Remitting Multiple Sclerosis in Paediatric Participants.2018. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2018-000516-22 (Accessed 8 May 2024).	RRMS but not in adults
2013-002318-11. Phase 3 Efficacy and Safety Study of BG00012 in Subjects With Relapsing-Remitting Multiple Sclerosis (RRMs).2014. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2013-002318-11 (Accessed 8 May 2024).	RRMS but not in adults
34882. *A Multicenter, Randomized, Rater-Blind, Parallel-Group, Active Controlled Study to Evaluate the Benefits of Switching Therapy (Glatiramer Acetate or Interferon β-1a) to Natalizumab in Subjects with Relapsing Remitting Multiple Sclerosis*.2010. URL: https://onderzoekmetmensen.nl/en/trial/34882 (Accessed 8 May 2024).	Terminated study
2016-000434-21. *PLENO – Open-label, Randomized, 2-arm, Active Comparator Study to Evaluate Safety and Tolerability in Portuguese Patients with Relapsing Remitting Multiple Sclerosis (MS) Transitioning from Current Subcutaneous Interferon Therapy to Peginterferon Beta 1a (PLEGRIDY™)*.2016. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2016-000434-21 (Accessed 8 May 2024).	Not informative to the network - compares against switch to chosen iDMT
Irct2013030512398N. The Effectiveness, Safety and Tolerability of Actoferon® Compared to Betaferon® in Subjects with Relapsing Remitting Multiple Sclerosis (RRMS).2014. URL: http://en.irct.ir/trial/12462 (Accessed 8 May 2024).	Not informative to the network - compares brands
Birnbaum G, Cree B, Altafullah I, Zinser M, Reder A. Combining beta interferon and atorvastatin may increase disease activity in multiple sclerosis. Neurology. 2008;71(18):1390-5. doi:10.1212/01.wnl.0000319698.40024.1c.	Not informative to the network - non DMT add on

Citation	Reason for exclusion
Boiko A, Bosenko L, Vasilovskii V, et al. A Comparative Placebo-Controlled Clinical Trial of the Efficacy and Safety of Interferon beta-1a Formulations for S.C. Administration in Patients with Remitting Multiple Sclerosis: First-Year Results. Neuroscience and Behavioral Physiology. 2018;48(7):883-889. doi:10.1007/s11055-018-0643-z.	Not informative to the network - compares brands
Boiko A, Lashch N, Sharanova S, et al. A Comparative Placebo-Controlled Clinical Trial of the Efficacy and Safety of Glatiramer Acetate 20 mg in Patients with Remitting Multiple Sclerosis: First-Year Study Results. Neuroscience and Behavioral Physiology. 2018;48(3):351-357. doi:10.1007/s11055-018-0570-z.	Not informative to the network - compares brands
Bonavita S, Dinacci D, Lavorgna L, et al. Treatment of multiple sclerosis with interferon beta in clinical practice: 2-year follow-up data from the South Italy Mobile MRI Project. Neurological sciences : official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology. 2006;27 Suppl 5:S365-8. doi:10.1007/s10072-006-0696-6.	Not a RCT
Bornstein M, Miller A, Slagle S. A pilot trial of cop 1 in exacerbating-remitting multiple sclerosis. New England Journal of Medicine. 1987;317(7):408-414. doi:10.1056/nejm198708133170703.	Did not evaluate intervention of interest
Boyko A, Bakhtiyarova K, Boyko O, et al. [Long-term Efficacy and Safety of Sampeginterferon-beta1a in the Treatment of Relapsing Remitting Multiple Sclerosis: a Randomized, Double-Blind Clinical Trial 104-Week Results]. Dolgosrochnye dannye po effektivnosti i bezopasnosti preparata sampeginterferon-beta1a u patsientov s remittiruyushchim rasseyannym sklerozom: rezul'taty 104-nedel'nogo randomizirovannogo dvoinogo slepogo klinicheskogo issledovaniya. 2023;123(2):52-59. doi:10.17116/jnevro202312302152.	Comparator not informative to the network
Boyko A, Bakhtiyarova K, Dudin V, et al. [The new pegylated interferon beta-1a (sampeginterferon beta-1a, BCD-054) in the treatment of remitting multiple sclerosis]. Novyi pegilirovannyi interferon beta-1a (sampeginterferon beta-1a, BCD-054) v terapii remittiruiushchego rasseiannogo skleroza. 2019;119(10. Vyp. 2):100-109. doi:10.17116/jnevro201911910100.	Comparator not informative to the network
Boyko A, Bosenko L, Vasilovskiy V, et al. [A comparative placebo-controlled clinical study on the efficacy and safety of interferon beta-1a for subcutaneous injections in patients with remitting multiple sclerosis: results of the first year of observations]. Sravnitel'noe platsebo-kontroliruemoe klinicheskoe issledovanie effektivnosti i bezopasnosti preparatov interferona beta-1a dlia podkozhnogo vvedeniia u patsientov s remittiruiushchim rasseiannym sklerozom: rezul'taty pervogo goda nabliudeniia. 2017;117(2. Vyp. 2):107-113. doi:10.17116/jnevro201711722107-113.	Not informative to the network - compares brands
Boyko A, Bosenko L, Vasilovskiy V, et al. Efficacy, tolerability and safety of the treatment with teberif: The results of a 2-year randomized clinical trial of treatment naive patients with remitting multiple sclerosis, who have not received dmt, after switching from other interferon beta-1a. Zhurnal Nevrologii i Psihiatrii imeni S.S. Korsakova. 2019;119(2):73-85. doi:10.17116/jnevro20191192273.	Not informative to the network - compares brands
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Citation	Reason for exclusion
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Citation	Reason for exclusion
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Citation	Reason for exclusion
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Citation	Reason for exclusion
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Citation	Reason for exclusion
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Durelli L, Verdun E, Barbero P, Bergui M, Versino E. Re: Vartanian T. An examination of the results of the EVIDENCE, INCOMIN, and phase III studies of interferon beta products in the treatment of multiple sclerosis. Clin Ther. 2003;25:105-118. Clinical therapeutics. 2003;25(6):1890-3. doi:10.1016/s0149-2918(03)90054-3.	Not a primary study
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Etemadifar M, Maghzi A, Hoseinzadeh A. Comparing side effects of CinnoVex with Avonex in relapsing remitting multiple sclerosis patients. Journal of Isfahan Medical School. 2009;27(93).	Not informative to the network - compares brands
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Citation	Reason for exclusion
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Fernandez O, Arbizu T, Izquierdo G, et al. Clinical benefits of interferon beta-1a in relapsing-remitting MS: a phase IV study. Acta neurologica Scandinavica. 2003;107(1):7-11. doi:10.1034/j.1600-0404.2003.01350.x.	Not a RCT
Fernandez O, Izquierdo G, Aguera E, et al. Comparison of first-line and second-line use of fingolimod in relapsing MS: The open-label EARLIMS study. Multiple sclerosis journal - experimental, translational and clinical. 2020;6(3):2055217320957358. doi:10.1177/2055217320957358.	Not a RCT
Filippi M, Wolinsky J, Comi G. Effects of oral glatiramer acetate on clinical and MRI-monitored disease activity in patients with relapsing multiple sclerosis: a multicentre, double-blind, randomised, placebo-controlled study. The Lancet. Neurology. 2006;5(3):213-20. doi:10.1016/s1474-4422(06)70327-1.	Did not evaluate intervention of interest - drug is of interest but in different presentation/dose than licensed
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Foley J, Defer G, Ryerson L, et al. Comparison of switching to 6-week dosing of natalizumab versus continuing with 4-week dosing in patients with relapsing-remitting multiple sclerosis (NOVA): a randomised, controlled, open-label, phase 3b trial. The Lancet. Neurology. 2022;21(7):608-619. doi:10.1016/s1474-4422(22)00143-0.	Not informative to the network - compares different protocols
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Francis G, Panitich H, Weinshenker B, Monaghan E, O'Connor P. Re: Vartanian T. An examination of the results of the EVIDENCE, INCOMIN, and phase III studies of interferon beta products in the treatment of multiple sclerosis. Clin Ther. 2003;25:105-118. Clinical therapeutics. 2003;25(6):1888-90. doi:10.1016/s0149-2918(03)90030-0.	Not a primary study
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Citation	Reason for exclusion
Freedman M, Wolinsky J, Truffinet P, et al. A randomized trial of teriflunomide added to glatiramer acetate in relapsing multiple sclerosis. Multiple sclerosis journal - experimental, translational and clinical. 2015;1:2055217315618687. doi:10.1177/2055217315618687.	Comparator not informative to the network
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Freedman M. Evidence of interferon beta-1a dose response in relapsing-remitting MS: The OWIMS study. Neurology. 1999;53(4):679-686. doi:10.1212/wnl.53.4.679.	Did not evaluate intervention of interest - drug is of interest but in different presentation/dose than licensed
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Citation	Reason for exclusion
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Citation	Reason for exclusion
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Citation	Reason for exclusion
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Citation	Reason for exclusion
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Honce J, Nair K, Sillau S, et al. Rituximab vs placebo induction prior to glatiramer acetate monotherapy in multiple sclerosis. Neurology. 2019;92(7):e723-e732. doi:10.1212/wnl.0000000000006916.	Not informative to the network - non DMT add on
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Citation	Reason for exclusion
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Jamroz-Wisniewska A, Zajdel R, Slowik A, et al. Modified Rio Score with Platform Therapy Predicts Treatment Success with Fingolimod and Natalizumab in Relapsing-Remitting Multiple Sclerosis Patients. Journal of clinical medicine. 2021;10(9). doi:10.3390/jcm10091830.	Not a RCT
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Citation	Reason for exclusion
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Citation	Reason for exclusion
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Khoury S, Healy B, Kivisakk P, et al. A randomized controlled double-masked trial of albuterol add-on therapy in patients with multiple sclerosis. Archives of neurology. 2010;67(9):1055-61. doi:10.1001/archneurol.2010.222.	Not informative to the network - non DMT add on
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Knobler R, Greenstein J, Johnson K, et al. A pilot trial of recombinant human beta interferon in the treatment of relapsing-remitting multiple sclerosis. Recent advances in Multiple Sclerosis therapy: proceedings of the Vth Congress of the European Committee for treatment and research in Multiple Sclerosis (ECTRIMS). ICS863. 1989;:121-124.	Exclude
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Citation	Reason for exclusion
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Kolind S, Abel S, Taylor C, et al. Myelin water imaging in relapsing multiple sclerosis treated with ocrelizumab and interferon beta-1a. NeuroImage. Clinical. 2022;35:103109. doi:10.1016/j.nicl.2022.103109.	Does not report on one of the outcomes of interest
Kondo T, Kawachi I, Onizuka Y, et al. Efficacy of dimethyl fumarate in Japanese multiple sclerosis patients: interim analysis of randomized, double-blind APEX study and its open-label extension. Multiple Sclerosis Journal - Experimental, Translational and Clinical. 2019;5(3). doi:10.1177/2055217319864974.	Did not evaluate intervention of interest
Koscielny V. Phase III SUNBEAM and RADIANCE PART B trials for Ozanimod in relapsing multiple sclerosis demonstrate superiority versus interferon-beta-1a (Avonex R) in reducing annualized relapse rates and MRI brain lesions. Neurodegenerative disease management. 2018;8(3):141-142. doi:10.2217/nmt-2018-0012.	Not a primary study
Kristoferitsch W, Seeldrayers P, Kyriallis K, et al. Double-blind randomized multicenter dose-comparison study of interferon-beta-1a (AVONEX): Rationale, design and baseline data. Multiple Sclerosis. 2001;7(3):179-183. doi:10.1191/135245801678438410.	Not informative to the network - drug of interest but not in a licensed dose
Krueger J, Kircik L, Hougeir F, et al. Cutaneous Adverse Events in the Randomized, Double-Blind, Active-Comparator DECIDE Study of Daclizumab High-Yield Process Versus Intramuscular Interferon Beta-1a in Relapsing-Remitting Multiple Sclerosis. Advances in therapy. 2016;33(7):1231-45. doi:10.1007/s12325-016-0353-2.	Comparator not informative to the network
Krupp L, Banwell B, Chitnis T, et al. Effect of fingolimod on health-related quality of life in paediatric patients with multiple sclerosis: results from the phase 3 PARADIGMS Study. BMJ neurology open. 2022;4(1):e000215. doi:10.1136/bmjno-2021-000215.	MS but not >90% RRMS
La Mantia L, Munari L, Lovati R. Glatiramer acetate for multiple sclerosis. The Cochrane database of systematic reviews. 2010;(5):CD004678. doi:10.1002/14651858.cd004678.pub2.	Review
Lampl C, Nagl S, Arnason B, et al. Efficacy and safety of interferon beta-1b sc in older RRMS patients--a posthoc analysis of the BEYOND study. Journal of neurology. 2013;260(7):1838-45. doi:10.1007/s00415-013-6888-0.	Not a RCT
Langdon D, Tomic D, Penner I, et al. Baseline characteristics and effects of fingolimod on cognitive performance in patients with relapsing-remitting multiple sclerosis. European journal of neurology. 2021;28(12):4135-4145. doi:10.1111/ene.15081.	Not a RCT
Lanzillo R, Quarantelli M, Pozzilli C, et al. No evidence for an effect on brain atrophy rate of atorvastatin add-on to interferon beta1b therapy in relapsing-remitting multiple sclerosis (the ARIANNA study). Multiple sclerosis (Houndmills, Basingstoke, England). 2016;22(9):1163-73. doi:10.1177/1352458515611222.	Not informative to the network - non DMT add on
Leist T, Cook S, Comi G, et al. Long-term safety data from the cladribine tablets clinical development program in multiple sclerosis. Multiple sclerosis and related disorders. 2020;46:102572. doi:10.1016/j.msard.2020.102572.	Not a RCT

Citation	Reason for exclusion
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Li D, Zhao G, Paty D. Randomized controlled trial of interferon-beta-1a in secondary progressive MS: MRI results. Neurology. 2001;56(11):1505-13. doi:10.1212/wnl.56.11.1505.	MS but not >90% RRMS
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Maciejowski M. Anti-CD20 monoclonal antibody in multiple sclerosis therapy: The results of phase 3 clinical studies on relapsing and primary progressive multiple sclerosis. Aktualnosci Neurologiczne. 2015;15(3):150-154. doi:10.15557/an.2015.0022.	Not a primary study
Mancardi G, Sormani M, Gualandi F, et al. Autologous hematopoietic stem cell transplantation in multiple sclerosis: a phase II trial. Neurology. 2015;84(10):981-8. doi:10.1212/wnl.0000000000001329.	MS but not >90% RRMS
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Massacesi L, Tramacere I, Amoroso S, et al. Azathioprine versus beta interferons for relapsing-remitting multiple sclerosis: a multicentre randomized non-inferiority trial. PloS one. 2014;9(11):e113371. doi:10.1371/journal.pone.0113371.	Did not evaluate intervention of interest
Mealli F, Mattei A, Mariottini A, Massacesi L. Non-inferiority analysis of subcutaneous versus intravenous 300 mg monthly natalizumab administration: A post hoc analysis of the REFINE study. Multiple sclerosis (Houndmills, Basingstoke, England). 2024;:13524585241238136. doi:10.1177/13524585241238136.	Not informative to the network - compares different protocols
2005-004289-18. A Multi-centre, Double Blind, Randomized, Placebo Controlled, Parallel Group Trial Investigating Minocycline versus placebo as add-on therapy in patients who are on treatment with Interferon-beta-1a 44mcg tiw (Rebif®) for the Treatment	Not informative to the network - non DMT add on

Citation	Reason for exclusion
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2010-020328-23. Supplementation of VigantOL® Oil versus Placebo as Add-on in Patients
with Relapsing-Remitting MS receiving Rebif® treatment.2010. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2010-020328-23 (Accessed 8 May 2024).	Not informative to the network - DMT add on
Metz L, Li D, Traboulsee A, et al. Glatiramer acetate in combination with minocycline in patients with relapsing--remitting multiple sclerosis: results of a Canadian, multicenter, double-blind, placebo-controlled trial. Multiple sclerosis (Houndmills, Basingstoke, England). 2009;15(10):1183-94. doi:10.1177/1352458509106779.	Not informative to the network - non DMT add on
Mikol D, Lopez-Bresnahan M, Taraskiewicz S, Chang P, Rangnow J. A randomized, multicentre, open-label, parallel-group trial of the tolerability of interferon beta-1a (Rebif) administered by autoinjection or manual injection in relapsing-remitting multiple sclerosis. Multiple sclerosis (Houndmills, Basingstoke, England). 2005;11(5):585-91. doi:10.1191/1352458505ms1197oa.	Not informative to the network - compares different protocols
Milanese C, Salmaggi A, La Mantia L, et al. Double blind study of intrathecal beta-interferon in multiple sclerosis: clinical and laboratory results. Journal of neurology, neurosurgery, and psychiatry. 1990;53(7):554-7. doi:10.1136/jnnp.53.7.554.	Did not evaluate intervention of interest
Miller D, Khan O, Sheremata W, et al. A controlled trial of natalizumab for relapsing multiple sclerosis. The New England journal of medicine. 2003;348(1):15-23. doi:10.1056/nejmoa020696.	Did not evaluate intervention of interest - drug is of interest but in different presentation/dose than licensed
Moccia M, Lanzillo R, Petruzzo M, et al. Single-Center 8-Years Clinical Follow-Up of Cladribine-Treated Patients From Phase 2 and 3 Trials. Frontiers in neurology. 2020;11:489. doi:10.3389/fneur.2020.00489.	Not a primary study

Citation	Reason for exclusion
Montalban X, Comi G, Antel J, et al. Long-term results from a phase 2 extension study of fingolimod at high and approved dose in relapsing multiple sclerosis. Journal of neurology. 2015;262(12):2627-34. doi:10.1007/s00415-015-7834-0.	Extension/expansion study
Montalban X, Comi G, O'Connor P, et al. Oral fingolimod (FTY720) in relapsing multiple sclerosis: impact on health-related quality of life in a phase II study. Multiple sclerosis (Houndmills, Basingstoke, England). 2011;17(11):1341-50. doi:10.1177/1352458511411061.	Extension/expansion study
Montalban X, Leist T, Cohen B, et al. Cladribine tablets added to IFN-beta in active relapsing MS. Neurology: Neuroimmunology and NeuroInflammation. 2018;5(5). doi:10.1212/nxi.0000000000000477.	Not informative to the network - DMT add on
Moore J, Massey J, Ford C, et al. Prospective phase II clinical trial of autologous haematopoietic stem cell transplant for treatment refractory multiple sclerosis. Journal of neurology, neurosurgery, and psychiatry. 2019;90(5):514-521. doi:10.1136/jnnp-2018-319446.	MS but not >90% RRMS
Nabavi S, Abolfazli R, Etemadrezaei A, et al. A Comparison Study of Efficacy and Safety of a Biosimilar Form of Intramuscular Betaeta-interferon I-a Versus the Reference Product: A Randomized Controlled Clinical Trial in Iran. Iranian journal of pharmaceutical research : IJPR. 2019;18(3):1632-1638. doi:10.22037/ijpr.2019.14503.12441.	Not informative to the network - compares brands
Nafissi S, Azimi A, Amini-Harandi A, Salami S, shahkarami M, Heshmat R. Comparing efficacy and side effects of a weekly intramuscular biogeneric/biosimilar interferon beta-1a with Avonex in relapsing remitting multiple sclerosis: a double blind randomized clinical trial. Clinical neurology and neurosurgery. 2012;114(7):986-9. doi:10.1016/j.clineuro.2012.02.039.	Not informative to the network - compares brands
Nakamura K, Mokliatchouk O, Arnold D, et al. Effects of Dimethyl Fumarate on Brain Atrophy in Relapsing-Remitting Multiple Sclerosis: Pooled Analysis Phase 3 DEFINE and CONFIRM Studies. Frontiers in Neurology. 2022;13:809273. doi:10.3389/fneur.2022.809273.	Did not evaluate intervention of interest
NCT01578330. A 12 -Month, Open-label, Multi-center Study to Explore the Health Outcomes of FTY720. URL: https://classic.clinicaltrials.gov/show/NCT01578330 (Accessed 8 May 2024).	Not a RCT
NCT01705236. A 3-year Multi-center Study to Describe Changes of OCT Parameters Under Treatment With Gilenya®. URL: https://classic.clinicaltrials.gov/show/NCT01705236 (Accessed 8 May 2024).	Not a RCT
NCT00451204. A Combination Trial of Copaxone Plus Estriol in Relapsing Remitting Multiple Sclerosis (RRMS). URL: https://classic.clinicaltrials.gov/show/NCT00451204 (Accessed 8 May 2024).	Did not evaluate intervention of interest
NCT01198132. A Multicentre Study of the Efficacy and Safety of Supplementary Treatment With Cholecalciferol in Patients With Relapsing Multiple Sclerosis Treated With Subcutaneous Interferon Beta-1a 44 µg 3 Times Weekly. URL: https://classic.clinicaltrials.gov/show/NCT01198132 (Accessed 8 May 2024).	Not informative to the network - non DMT add on
NCT01404117. A Multinational, Randomized, Double-blind, Parallel-group, Placebo-controlled Study Assessing the Safety and Tolerability. URL: https://classic.clinicaltrials.gov/show/NCT01404117 (Accessed 8 May 2024).	Not informative to the network - DMT add on

Citation	Reason for exclusion
NCT03283397. A Phase IIIb, Multicenter, International Study to Evaluate the Efficacy, Safety and Tolerability of EK-12 in Patients With RRMS. URL: https://classic.clinicaltrials.gov/show/NCT03283397 (Accessed 8 May 2024).	Comparator not informative to the network
NCT01142466. A Phase IV Study of Rebif ® 44mcg Administered Three Times Per Week by Subcutaneous Injection Compared With no Treatment in the Therapy of Relapsing Multiple Sclerosis After Mitoxantrone. URL: https://classic.clinicaltrials.gov/show/NCT01142466 (Accessed 8 May 2024).	Not informative to the network - non DMT add on
NCT03387046. A Pilot Study in Participants With Relapsing Remitting Multiple Sclerosis (RR-MS). URL: https://classic.clinicaltrials.gov/show/NCT03387046 (Accessed 8 May 2024).	Not informative to the network - non DMT add on
NCT00292266. A Study of Rebif® Compared With Avonex® in the Treatment of Relapsing-remitting Multiple Sclerosis (MS). URL: https://classic.clinicaltrials.gov/show/NCT00292266 (Accessed 8 May 2024).	Not informative to the network - compares brands
NCT02064816. A Study of Rebif® in Subjects With Relapsing Multiple Sclerosis. URL: https://classic.clinicaltrials.gov/show/NCT02064816 (Accessed 8 May 2024).	Not informative to the network - compares different protocols
NCT04121221. A Study to Asses Efficacy, Safety and Tolerability of Monthly Long-acting IM Injection of GA Depot in Subjects With RMS. URL: https://classic.clinicaltrials.gov/show/NCT04121221 (Accessed 8 May 2024).	Did not evaluate intervention of interest - drug is of interest but in different presentation/dose than licensed
NCT01975298. A Study to Evaluate 2 Doses Of Oral Administration Of Laquinimod Compared to Interferon ß-1a Administered by Injection in Participants With Relapsing Remitting Multiple Sclerosis (RRMS). URL: https://classic.clinicaltrials.gov/show/NCT01975298 (Accessed 8 May 2024).	Comparator not informative to the network
NCT03368664. A Study to Evaluate Efficacy, Safety, and Tolerability of Alemtuzumab in Pediatric Patients With RRMS With Disease Activity on Prior DMT. URL: https://classic.clinicaltrials.gov/show/NCT03368664 (Accessed 8 May 2024).	RRMS but not in adults
NCT03689972. A Study to Evaluate Efficacy, Safety, and Tolerability of EID of Natalizumab (BG00002) in Participants With RRMS Switching From Treatment With Natalizumab SID in Relation to Continued SID Treatment- Followed by Extension Study Comprising SC and IV Natalizumab Administration. URL: https://classic.clinicaltrials.gov/show/NCT03689972 (Accessed 8 May 2024).	Not informative to the network - compares different protocols
NCT05265728. A Study to Evaluate Efficacy, Safety, Pharmacokinetics, and Pharmacodynamics of Multiple Doses of Natalizumab (BG00002) Administered Subcutaneously to Japanese Participants With Relapsing-Remitting Multiple Sclerosis. URL: https://classic.clinicaltrials.gov/show/NCT05265728 (Accessed 8 May 2024).	Not a RCT
NCT05123703. A Study To Evaluate Safety And Efficacy Of Ocrelizumab In Comparison With Fingolimod In Children And Adolescents With Relapsing-Remitting Multiple Sclerosis. URL: https://classic.clinicaltrials.gov/show/NCT05123703 (Accessed 8 May 2024).	RRMS but not in adults
NCT00203086. A Study to Evaluate the Long Term Safety and Effectiveness of Novantrone Therapy Followed by Copaxone Treatment for Multiple Sclerosis. URL: https://classic.clinicaltrials.gov/show/NCT00203086 (Accessed 8 May 2024).	Not a RCT

Citation	Reason for exclusion
NCT00203073. A Study to Evaluate the Safety and Effectiveness of Novantrone Therapy Followed by Copaxone for Multiple Sclerosis. URL: https://classic.clinicaltrials.gov/show/NCT00203073 (Accessed 8 May 2024).	Not informative to the network - non DMT add on
NCT03958877. A Study to Evaluate the Safety, Tolerability, and Efficacy of BIIB017 (Peginterferon Beta-1a) in Pediatric Participants for the Treatment of Relapsing-Remitting Multiple Sclerosis. URL: https://classic.clinicaltrials.gov/show/NCT03958877 (Accessed 8 May 2024).	RRMS but not in adults
NCT00202982. A Study to Test the Effectiveness and Safety of a New Higher 40mg Dose of Copaxone® Compared to Copaxone® 20mg, the Currently Approved Dose. URL: https://classic.clinicaltrials.gov/show/NCT00202982 (Accessed 8 May 2024).	Not informative to the network - drug of interest but not in a licensed dose
NCT00883337. A Study Comparing the Effectiveness and Safety of Teriflunomide and Interferon Beta-1a in Patients With Relapsing Multiple Sclerosis. URL: https://classic.clinicaltrials.gov/show/NCT00883337 (Accessed 8 May 2024).	Comparator not informative to the network
NCT01395316. Alemtuzumab on Surrogate Markers of Disease Activity and Repair Using Advanced MRI Measures in Subjects With Relapsing Remitting Multiple Sclerosis. URL: https://classic.clinicaltrials.gov/show/NCT01395316 (Accessed 8 May 2024).	Not a RCT
NCT00206648. An Efficacy and Safety Comparison Study of Two Marketed Drugs in Patients With Relapsing-remitting MS. URL: https://classic.clinicaltrials.gov/show/NCT00206648 (Accessed 8 May 2024).	Did not evaluate intervention of interest
NCT01578785. An Efficacy, Safety and Tolerability Study of Glatiramer Acetate (GA) 20 mg/0.5 ml New Formulation Administered Daily by Subcutaneous (SC) Injection in Subjects With Relapsing-Remitting Multiple Sclerosis (RRMS). URL: https://classic.clinicaltrials.gov/show/NCT01578785 (Accessed 8 May 2024).	Terminated study
NCT00930553. An Extension Protocol for Multiple Sclerosis Patients Who Participated in Genzyme-Sponsored Studies of Alemtuzumab. URL: https://classic.clinicaltrials.gov/show/NCT00930553 (Accessed 8 May 2024).	Extension/expansion study
NCT06228781. Autologous Hematopoietic Stem Cell Transplantation for Refractory Multiple Sclerosis. URL: https://classic.clinicaltrials.gov/show/NCT06228781 (Accessed 8 May 2024).	Not a RCT
NCT00168766. Avonex (Interferon-beta-1a) and Avonex Plus Methylprednisolone for the Treatment of Relapsing-remitting MS. URL: https://classic.clinicaltrials.gov/show/NCT00168766 (Accessed 8 May 2024).	Did not evaluate intervention of interest
NCT00459667. BEYOND Follow-up: Betaferon®/Betaseron® Efficacy Yielding Outcomes of a New Dose. URL: https://classic.clinicaltrials.gov/show/NCT00459667 (Accessed 8 May 2024).	Did not evaluate intervention of interest - drug is of interest but in different presentation/dose than licensed
NCT00893217. BEYOND Pilot Study. URL: https://classic.clinicaltrials.gov/show/NCT00893217 (Accessed 8 May 2024).	Did not evaluate intervention of interest - drug is of interest but in different presentation/dose than licensed

Citation	Reason for exclusion
NCT00099502. BEYOND: Betaferon/Betaseron Efficacy Yielding Outcomes of a New Dose in Multiple Sclerosis (MS) Patients. URL: https://classic.clinicaltrials.gov/show/NCT00099502 (Accessed 8 May 2024).	Did not evaluate intervention of interest
NCT01156311. BG00012 Phase 2 Combination Study in Participants With Multiple Sclerosis. URL: https://classic.clinicaltrials.gov/show/NCT01156311 (Accessed 8 May 2024).	Did not evaluate intervention of interest
NCT00605215. BRAVO Study: Laquinimod Double-blind Placebo-controlled Study in Participants With Relapsing-Remitting Multiple Sclerosis (RRMS) With a Rater Blinded Reference Arm of Interferon β-1a (Avonex®). URL: https://classic.clinicaltrials.gov/show/NCT00605215 (Accessed 8 May 2024).	Did not evaluate intervention of interest
NCT00641537. *CLARITY Extension Study*. URL: https://classic.clinicaltrials.gov/show/NCT00641537 (Accessed 8 May 2024).	Extension/expansion study
NCT01006265. Clinical Study to Evaluate the Efficacy, Safety, and Tolerability of ACT-128800 in Patients With Relapsing-remitting Multiple Sclerosis. URL: https://classic.clinicaltrials.gov/show/NCT01006265 (Accessed 8 May 2024).	Did not evaluate intervention of interest
NCT01093326. Clinical Study to Investigate the Long-term Safety, Tolerability, and Efficacy of Ponesimod in Patients With Relapsing-remitting Multiple Sclerosis. URL: https://classic.clinicaltrials.gov/show/NCT01093326 (Accessed 8 May 2024).	Did not evaluate intervention of interest
NCT00337779. Clinical Trial Comparing Treatment of Relapsing-Remitting Multiple Sclerosis (RR-MS) With Two Doses of Glatiramer Acetate (GA). URL: https://classic.clinicaltrials.gov/show/NCT00337779 (Accessed 8 May 2024).	Not informative to the network - drug of interest but not in a licensed dose
NCT00211887. Combination Therapy in Patients With Relapsing-Remitting Multiple Sclerosis (MS)CombiRx. URL: https://classic.clinicaltrials.gov/show/NCT00211887 (Accessed 8 May 2024).	Did not evaluate intervention of interest - drug is of interest but in different presentation/dose than licensed
NCT00298662. Combination Therapy of Betaseron-Prograf in Multiple Sclerosis. URL: https://classic.clinicaltrials.gov/show/NCT00298662 (Accessed 8 May 2024).	Did not evaluate intervention of interest
NCT00618527. Combination Therapy Using Cellcept and Rebif in RRMS. URL: https://classic.clinicaltrials.gov/show/NCT00618527 (Accessed 8 May 2024).	Not informative to the network - non DMT add on
NCT02744222. Comparative Clinical Trial to Evaluate Efficacy, Safety and Tolerance of BCD-054 and Avonex® for Treatment of Patients With Remitting-relapsing Multiple Sclerosis. URL: https://classic.clinicaltrials.gov/show/NCT02744222 (Accessed 8 May 2024).	Did not evaluate intervention of interest
NCT03535298. Determining the Effectiveness of early Intensive Versus Escalation Approaches for RRMS. URL: https://classic.clinicaltrials.gov/show/NCT03535298 (Accessed 8 May 2024).	Did not evaluate intervention of interest
NCT05902429. Effects of Oral Cladribine on Remyelination and Inflammation in Multiple Sclerosis Patients. URL: https://classic.clinicaltrials.gov/show/NCT05902429 (Accessed 8 May 2024).	Not a RCT

Citation	Reason for exclusion
NCT02753088. Efficacy and Safety of BCD-063 and Copaxone-Teva in Patients With Relapsing-Remitting Multiple Sclerosis. URL: https://classic.clinicaltrials.gov/show/NCT02753088 (Accessed 8 May 2024).	Not informative to the network - compares brands
NCT01064401. Efficacy and Safety of BIIB019 (Daclizumab High Yield Process) Versus Interferon β 1a in Participants With Relapsing-Remitting Multiple Sclerosis. URL: https://classic.clinicaltrials.gov/show/NCT01064401 (Accessed 8 May 2024).	Did not evaluate intervention of interest
NCT02881567. Efficacy and Safety of Daclizumab in Participants With RRMS Switching From Natalizumab. URL: https://classic.clinicaltrials.gov/show/NCT02881567 (Accessed 8 May 2024).	Did not evaluate intervention of interest
NCT00333138. Efficacy and Safety of FTY720 in Patients With Relapsing Multiple Sclerosis. URL: https://classic.clinicaltrials.gov/show/NCT00333138 (Accessed 8 May 2024).	MS but not >90% RRMS
NCT05242133. Efficacy and Safety of Peginterferon Beta-1a (CinnaGen) in Participants With Relapsing Remitting Multiple Sclerosis. URL: https://classic.clinicaltrials.gov/show/NCT05242133 (Accessed 8 May 2024).	Did not evaluate intervention of interest
NCT04115488. Efficacy and Safety of the Biosimilar Natalizumab PB006 in Comparison to Tysabri®. URL: https://classic.clinicaltrials.gov/show/NCT04115488 (Accessed 8 May 2024).	Did not evaluate intervention of interest
NCT00451451. Efficacy and Safety Study of Oral BG00012 With Active Reference in Relapsing-Remitting Multiple Sclerosis. URL: https://classic.clinicaltrials.gov/show/NCT00451451 (Accessed 8 May 2024).	Did not evaluate intervention of interest
NCT01111656. Efficacy, Safety and Tolerability of Atorvastatin 40 mg in Patients With Relapsing-remitting Multiple Sclerosis Treated With Interferon-beta-1b. URL: https://classic.clinicaltrials.gov/show/NCT01111656 (Accessed 8 May 2024).	Not informative to the network - non DMT add on
NCT01963611. Efficacy, Safety, and Tolerability of Plovamer Acetate (Pathway 1). URL: https://classic.clinicaltrials.gov/show/NCT01963611 (Accessed 8 May 2024	Did not evaluate intervention of interest
NCT03177083. Evaluate Safety/Tolerability in Portuguese Participants With RRMS Transitioning From Current Therapy. URL: https://classic.clinicaltrials.gov/show/NCT03177083 (Accessed 8 May 2024).	Comparator not informative to the network
NCT01333358. Evaluating Alemtuzumab as a Treatment in Stabilizing Neurocognitive Function In Relapsing Remitting Multiple Sclerosis Patients. URL: https://classic.clinicaltrials.gov/show/NCT01333358 (Accessed 8 May 2024).	Does not report on one of the outcomes of interest
NCT02939079. Evaluating of the Effect of Fingolimod With Fish Oil on Relapsing-Remitting Multiple Sclerosis Patients. URL: https://classic.clinicaltrials.gov/show/NCT02939079 (Accessed 8 May 2024).	Not informative to the network - non DMT add on
NCT00219908. Evaluation of a New Therapeutic Strategy in Early and Active Relapsing-Remitting Multiple Sclerosis. URL: https://classic.clinicaltrials.gov/show/NCT00219908 (Accessed 8 May 2024).	Did not evaluate intervention of interest
NCT01534182. Evaluation of Patient Reported Outcomes in RRMS Patients Candidates for MS Therapy Change and Transitioned to Fingolimod 0.5 mg (EPOC). URL: https://classic.clinicaltrials.gov/show/NCT01534182 (Accessed 8 May 2024).	Extension/expansion study
NCT01623596. Evaluation of Patient Retention of Fingolimod vs. Currently Approved Disease Modifying Therapy in Patients With Relapsing Remitting Multiple Sclerosis. URL: https://classic.clinicaltrials.gov/show/NCT01623596 (Accessed 8 May 2024).	Not a RCT

Citation	Reason for exclusion
NCT01167426. Evaluation of Two Glatiramer Acetate (GA) Formulations in Relapsing-Remitting Multiple Sclerosis (RRMS) Patients. URL: https://classic.clinicaltrials.gov/show/NCT01167426 (Accessed 8 May 2024).	Not a RCT
NCT01405820. Exploratory Study of the Safety, Tolerability and Efficacy of Multiple Regimens of Natalizumab in Adult Participants With Relapsing Multiple Sclerosis (MS). URL: https://classic.clinicaltrials.gov/show/NCT01405820 (Accessed 8 May 2024).	Not informative to the network - drug of interest but not in a licensed dose
NCT01020370. Exploratory Study to Investigate the Reparative and Regenerative Potential of Alemtuzumab in Relapsing-Remitting Multiple Sclerosis Patients Participating in the CARE MS I and MS II Studies. URL: https://classic.clinicaltrials.gov/show/NCT01020370 (Accessed 8 May 2024).	Not a RCT
NCT00235989. Extension of Prior Study Evaluating Safety and Tolerability of Two Doses of Betaseron® to Treat Relapsing-remitting Multiple Sclerosis. URL: https://classic.clinicaltrials.gov/show/NCT00235989 (Accessed 8 May 2024).	Not a RCT
NCT01416155. Extension Study to Evaluate Safety and Efficacy of Natalizumab in Japanese Participants With Relapsing-Remitting Multiple Sclerosis. URL: https://classic.clinicaltrials.gov/show/NCT01416155 (Accessed 8 May 2024).	Extension/expansion study
NCT03345940. Fingolimod Versus Dimethyl-fumarate in Multiple Sclerosis. URL: https://classic.clinicaltrials.gov/show/NCT03345940 (Accessed 8 May 2024).	Comparator not informative to the network
NCT00623415. Flupirtine as Oral Treatment in Multiple Sclerosis. URL: https://classic.clinicaltrials.gov/show/NCT00623415 (Accessed 8 May 2024).	Did not evaluate intervention of interest
NCT00203021. Glatiramer Acetate (Copaxone®) Study to Follow Participants From the First Original Study for Safety and Effectiveness. URL: https://classic.clinicaltrials.gov/show/NCT00203021 (Accessed 8 May 2024).	Not a RCT
NCT01456416. Glatiramer Acetate for Multiple Sclerosis With Autoimmune Comorbidities. URL: https://classic.clinicaltrials.gov/show/NCT01456416 (Accessed 8 May 2024).	Not a RCT
NCT00939549. High Dose Cyclophosphamide Followed by Glatiramer Acetate in the Treatment of Relapsing Remitting Multiple Sclerosis. URL: https://classic.clinicaltrials.gov/show/NCT00939549 (Accessed 8 May 2024).	Not informative to the network - non DMT add on
NCT00288626. High-Dose Immunosuppression and Autologous Transplantation for Multiple Sclerosis (HALT MS) Study. URL: https://classic.clinicaltrials.gov/show/NCT00288626 (Accessed 8 May 2024).	Not informative to the network - non DMT add on
NCT00662649. Long-term Efficacy and Safety of Fingolimod (FTY720) in Patients With Relapsing-remitting Multiple Sclerosis. URL: https://classic.clinicaltrials.gov/show/NCT00662649 (Accessed 8 May 2024).	Extension/expansion study
NCT01797965. Long-Term Extension Study in Participants With Multiple Sclerosis Who Have Completed Study 205MS301 (NCT01064401) to Evaluate the Safety and Efficacy of BIIB019. URL: https://classic.clinicaltrials.gov/show/NCT01797965 (Accessed 8 May 2024).	Extension/expansion study
NCT02307838. Long-term Follow-up of Fingolimod Phase II Study Patients. URL: https://classic.clinicaltrials.gov/show/NCT02307838 (Accessed 8 May 2024).	Not a RCT

Citation	Reason for exclusion
NCT03961204. Long-Term Outcomes and Durability of Effect Following Treatment With Cladribine Tablets for MS (CLASSIC-MS). URL: https://classic.clinicaltrials.gov/show/NCT03961204 (Accessed 8 May 2024).	Not a RCT
NCT01134627. Minocycline as add-on to Interferon Beta-1a IFN Beta-1a (Rebif®) in Relapsing-Remitting Multiple Sclerosis RRMS. URL: https://classic.clinicaltrials.gov/show/NCT01134627 (Accessed 8 May 2024).	Not informative to the network - non DMT add on
NCT00097760. Natalizumab in Combination With Glatiramer Acetate (GA) in Patients With Relapsing-Remitting Multiple Sclerosis. URL: https://classic.clinicaltrials.gov/show/NCT00097760 (Accessed 8 May 2024).	Not informative to the network - DMT add on
NCT04971005. Ocrelizumab or Alemtuzumab Compared With Autologous Hematopoietic Stem Cell Transplantation in Multiple Sclerosis - a Phase-2 Randomised Controlled Trial. URL: https://classic.clinicaltrials.gov/show/NCT04971005 (Accessed 8 May 2024).	Terminated study
NCT00473213. Optimizing IFN Beta - 1B Dose. URL: https://classic.clinicaltrials.gov/show/NCT00473213 (Accessed 8 May 2024).	Not informative to the network - compares different protocols
NCT01317004. Patients With Relapse Remitting Multiple Sclerosis (RRMS): Candidates for MS Therapy Change. URL: https://classic.clinicaltrials.gov/show/NCT01317004 (Accessed 8 May 2024).	Not informative to the network - compares against switch to chosen iDMT
NCT01464905. Phase 3 Study to Evaluate Efficacy and Safety of NU100 in Patients With Relapsing Remitting Multiple Sclerosis (RRMS). URL: https://classic.clinicaltrials.gov/show/NCT01464905 (Accessed 8 May 2024).	Did not evaluate intervention of interest
NCT02255656. Phase IIIB-IV Long-Term Follow-up Study for Patients Who Participated in CAMMS03409. URL: https://classic.clinicaltrials.gov/show/NCT02255656 (Accessed 8 May 2024).	Not a RCT
NCT00202995. Randomized Study Designed to Look at Disease Progression Using 2 Currently FDA Approved Drugs for the Treatment of RRMS. URL: https://classic.clinicaltrials.gov/show/NCT00202995 (Accessed 8 May 2024).	No results found
NCT00428584. RNF and Betaseron® Tolerability Study. URL: https://classic.clinicaltrials.gov/show/NCT00428584 (Accessed 8 May 2024).	Does not report on one of the outcomes of interest
NCT05423769. Safety and Effectiveness of Generic Fingolimod (Sphingomod®, Hikma) in Patients With Relapsing-Remitting Multiple Sclerosis in Egypt. URL: https://classic.clinicaltrials.gov/show/NCT05423769 (Accessed 8 May 2024).	Not a RCT
NCT00324506. Safety and Efficacy of Cellcept and Avonex as Combination Treatment in Multiple Sclerosis. URL: https://classic.clinicaltrials.gov/show/NCT00324506 (Accessed 8 May 2024).	Not informative to the network - non DMT add on
NCT01941004. Safety and Efficacy of Fingolimod in MS Patients in China. URL: https://classic.clinicaltrials.gov/show/NCT01941004 (Accessed 8 May 2024).	Withdrawn study
NCT02142205. Safety and Efficacy of Natalizumab (BG00002, Tysabri®) in Russian Participants With Relapsing Remitting Multiple Sclerosis (RRMS). URL: https://classic.clinicaltrials.gov/show/NCT02142205 (Accessed 8 May 2024).	Not a RCT

Citation	Reason for exclusion
NCT00030966. Safety and Efficacy of Natalizumab in Combination With Avonex in the Treatment of Multiple Sclerosis. URL: https://classic.clinicaltrials.gov/show/NCT00030966 (Accessed 8 May 2024).	Not informative to the network - DMT add on
NCT00203112. Safety and Efficacy Study of Copaxone Administered in Combination With Minocycline. URL: https://classic.clinicaltrials.gov/show/NCT00203112 (Accessed 8 May 2024).	Not informative to the network - non DMT add on
NCT00203099. Safety and Efficacy Study of Copaxone Administered in Combination With N-Acetylcysteine. URL: https://classic.clinicaltrials.gov/show/NCT00203099 (Accessed 8 May 2024).	Not informative to the network - non DMT add on
NCT00246324. Safety and Efficacy Study of Doxycycline in Combination With Interferon-B-1a to Treat Multiple Sclerosis. URL: https://classic.clinicaltrials.gov/show/NCT00246324 (Accessed 8 May 2024).	Not informative to the network - non DMT add on
NCT04480853. Safety and Efficacy Study of Fingolimod in Taiwanese Adults (≥ 20years) With Relapsing Remitting Multiple Sclerosis. URL: https://classic.clinicaltrials.gov/show/NCT04480853 (Accessed 8 May 2024).	Not a RCT
NCT01497262. Safety and Tolerability of Fingolimod in Patients With Relapsing-remitting Multiple Sclerosis. URL: https://classic.clinicaltrials.gov/show/NCT01497262 (Accessed 8 May 2024).	Not a RCT
NCT01874145. Safety and Tolerability of Glatiramer Acetate. URL: https://classic.clinicaltrials.gov/show/NCT01874145 (Accessed 8 May 2024).	Not informative to the network - compares different protocols
NCT00151801. Safety and Tolerability of Interferon-Beta-1a and Estroprogestins Association in MS Patients. URL: https://classic.clinicaltrials.gov/show/NCT00151801 (Accessed 8 May 2024).	Not informative to the network - non DMT add on
NCT00947752. Safety of New Formulation of Glatiramer Acetate. URL: https://classic.clinicaltrials.gov/show/NCT00947752 (Accessed 8 May 2024).	Not informative to the network - compares different protocols
NCT00317941. Safety Study in Relapsing-remitting Multiple Sclerosis (RRMS) Patients Receiving Betaferon or Rebif. URL: https://classic.clinicaltrials.gov/show/NCT00317941 (Accessed 8 May 2024).	Not informative to the network - compares brands
NCT00559702. Safety Study of Natalizumab to Treat Multiple Sclerosis (MS). URL: https://classic.clinicaltrials.gov/show/NCT00559702 (Accessed 8 May 2024).	Not informative to the network - compares different protocols
NCT01808885. Safety Study of Olesoxime in Patients With Stable Relapsing Remitting Multiple Sclerosis Treated With Interferon Beta. URL: https://classic.clinicaltrials.gov/show/NCT01808885 (Accessed 8 May 2024).	Did not evaluate intervention of interest
NCT00429442. Simvastatin as an add-on Treatment to Copaxone for the Treatment of Relapsing Multiple Sclerosis. URL: https://classic.clinicaltrials.gov/show/NCT00429442 (Accessed 8 May 2024).	Not informative to the network - non DMT add on
NCT00492765. Simvastatin as an Add-on Treatment to Interferon-beta-1a for the Treatment of Relapsing-Remitting Multiple Sclerosis. URL: https://classic.clinicaltrials.gov/show/NCT00492765 (Accessed 8 May 2024).	Not informative to the network - non DMT add on
NCT02727907. Study of Efficacy and Safety of Drugs BCD-033 and Rebif for Treatment of Patients With Multiple Sclerosis. URL: https://classic.clinicaltrials.gov/show/NCT02727907 (Accessed 8 May 2024).	Not informative to the network - compares brands

Citation	Reason for exclusion
NCT04032158. Study of Evobrutinib in Participants With Relapsing Multiple Sclerosis (RMS). URL: https://classic.clinicaltrials.gov/show/NCT04032158 (Accessed 8 May 2024).	Terminated study
NCT04032171. Study of Evobrutinib in Participants With RMS. URL: https://classic.clinicaltrials.gov/show/NCT04032171 (Accessed 8 May 2024).	Terminated study
NCT01772199. Study to Assess Whether GSK239512 Can Remyelinate Lesions in Subjects With Relapsing Remitting Multiple Sclerosis. URL: https://classic.clinicaltrials.gov/show/NCT01772199 (Accessed 8 May 2024).	Did not evaluate intervention of interest
NCT00525668. Sunphenon Epigallocatechin-gallate (EGCg) in Relapsing-remitting Multiple Sclerosis (SuniMS Study). URL: https://classic.clinicaltrials.gov/show/NCT00525668 (Accessed 8 May 2024).	Did not evaluate intervention of interest
NCT01285401. Supplementation of VigantOL® Oil Versus Placebo as Add-on in Patients With Relapsing Remitting Multiple Sclerosis Receiving Rebif® Treatment. URL: https://classic.clinicaltrials.gov/show/NCT01285401 (Accessed 8 May 2024).	Not informative to the network - non DMT add on
NCT01005095. The Effects of Interferon Beta Combined With Vitamin D on Relapsing Remitting Multiple Sclerosis Patients. URL: https://classic.clinicaltrials.gov/show/NCT01005095 (Accessed 8 May 2024).	Not informative to the network - non DMT add on
NCT03500328. Traditional Versus Early Aggressive Therapy for Multiple Sclerosis Trial. URL: https://classic.clinicaltrials.gov/show/NCT03500328 (Accessed 8 May 2024).	Did not evaluate intervention of interest
NCT00039988. Treatment of Multiple Sclerosis With Copaxone and Albuterol. URL: https://classic.clinicaltrials.gov/show/NCT00039988 (Accessed 8 May 2024).	Not informative to the network - non DMT add on
2004-004903-39. A pilot multi-centre randomised controlled trial of sequential treatment with Mitoxantrone and Glatiramer Acetate vs. Interferon Beta-1a in early active relapsing remitting Multiple Sclerosis. https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2004-004903-39 (Accessed 8 May 2024).	Not informative to the network - DMT add on
Newsome S, Kieseier B, Arnold D, et al. Subgroup and sensitivity analyses of annualized relapse rate over 2 years in the ADVANCE trial of peginterferon beta-1a in patients with relapsing-remitting multiple sclerosis. Journal of neurology. 2016;263(9):1778-87. doi:10.1007/s00415-016-8182-4.	Extension/expansion study
Newsome S, Mokliatchouk O, Castrillo-Viguera C, Naylor M. Matching-adjusted comparisons demonstrate better clinical outcomes in patients with relapsing multiple sclerosis treated with peginterferon beta-1a than with teriflunomide. Multiple sclerosis and related disorders. 2020;40:101954. doi:10.1016/j.msard.2020.101954.	Not a primary study
Newsome S, Scott T, Arnold D, et al. Long-term outcomes of peginterferon beta-1a in multiple sclerosis: results from the ADVANCE extension study, ATTAIN. Therapeutic advances in neurological disorders. 2018;11:1756286418791143. doi:10.1177/1756286418791143.	Extension/expansion study
2012-003735-32. Study to compare the efficacy and/or safety of masitinib at 3 mg/kg/day with switch to 4.5 then to 6 mg/kg/day to interferon beta-1a, interferon beta-1b, peginterferon beta-1a or glatiramer acetate in patients with relapsing remitting	Comparator not informative to the network

Citation	Reason for exclusion
multiple sclerosis with unsatisfactory response to these first line treatments.2015. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2012-003735-32 (Accessed 8 May 2024).	
2011-000150-31. EFFECTS OF GLATIRAMER ACETATE ON TISSUE DAMAGE, CORTICAL FUNCTIONS AND FATIGUE IN MULTIPLE SCLEROSIS: A MORPHO-FUNCTIONAL MRI STUDY.2011. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2011-000150-31 (Accessed 8 May 2024).	Not a RCT
2016-000708-26. ND.2021. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2016-000708-26 (Accessed 8 May 2024).	Not a RCT
2008-000955-90. Randomized, single-blind, clinical and MRI study for evaluation of safety and efficacy of N-Acetyl Cysteine (NAC) associated with high-dose beta-Interferon in Relapsing-Remitting (RR) multiple sclerosis patients - renac.2008. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2008-000955-90 (Accessed 8 May 2024).	Not informative to the network - non DMT add on
2011-000770-60. An open-label, multi-center, expanded access study with fingolimod in patients with relapsing-remitting multiple sclerosis for whom no suitable therapy exists.- ND.2011. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2011-000770-60 (Accessed 8 May 2024).	Not a RCT
RPCEC00000197. Itolizumab for Relapsing Remitting Multiple Sclerosis.2015. URL: https://rpcec.sld.cu/en/trials/RPCEC00000197-En (Accessed 8 May 2024).	Did not evaluate intervention of interest
Per-002-12. *A 4-Month, Open-Label, Multicenter Study To Explore The Safety And Tolerability Of Fingolimod 0.5 Mg In Patients With Relapsing-Remitting Multiple Sclerosis*.2012. URL: https://www.ins.gob.pe/ensayosclinicos/rpec/recuperarECPBNuevoEN.asp?numec=002-12 (Accessed 8 May 2024).	Not a RCT
2007-004122-24. *An extension of the 24-month, double-blind, randomized, multicenter, placebo-controlled, parallel-group study comparing efficacy and safety of FTY720 1.25 mg and 0.5 mg administered orally once daily versus placebo in patients with relapsing-remitting multiple sclerosis*.2007. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2007-004122-24 (Accessed 8 May 2024).	Extension/expansion study
2012-000674-31. A 3-year, multi-center study to describe the long term changes of optical coherence tomography (OCT) parameters in patients under treatment with Gilenya®.2012. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2012-000674-31 (Accessed 8 May 2024).	Not a RCT
2011-002969-38. *A 6-month, multicenter, randomized, controlled parallel group study to evaluate the effect of physical training on fatigue in patients with relapsing-remitting multiple sclerosis treated with fingolimod (Gilenya®), followed by a 6 month optional extension phase*.2011. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2011-002969-38 (Accessed 8 May 2024).	Did not evaluate intervention of interest
2011-001692-39. *A study to evaluate the safety and tolerability of the combination of an antidepressive therapy with oral fingolimod in the treatment of relapsing remitting multiple sclerosis patients with mild to moderate depression*.2011. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2011-001692-39 (Accessed 8 May 2024).	Did not evaluate intervention of interest

Citation	Reason for exclusion
2011-001442-15. A study to evaluate disease control and safety in patients with RRMS switching from natalizumab to fingolimod.2011. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2011-001442-15 (Accessed 8 May 2024).	Not a RCT
NCT04940065. Special Drug-use Surveillance for Kesimpta for s.c. Injection 20 mg Pen.2021. URL: https://clinicaltrials.gov/ct2/show/NCT04940065 (Accessed 8 May 2024).	Not an RCT
O'Connor P, Comi G, Montalban X, et al. Oral fingolimod (FTY720) in multiple sclerosis: two-year results of a phase II extension study. Neurology. 2009;72(1):73-9. doi:10.1212/01.wnl.0000338569.32367.3d.	Extension/expansion study
O'Connor P, Goodman A, Willmer-Hulme A, et al. Randomized multicenter trial of natalizumab in acute MS relapses: clinical and MRI effects. Neurology. 2004;62(11):2038-43. doi:10.1212/01.wnl.0000128136.79044.d6.	Did not evaluate intervention of interest - drug is of interest but in different presentation/dose than licensed
O'Connor P. Interferon-beta1a reduced relapses at 2 years in relapsing-remitting multiple sclerosis. Evidence-Based Medicine. 1999;4(3):74-75. doi:10.1136/ebm.1999.4.74.	Not a primary study
NCT04688788. *Non-inferiority Study of Ocrelizumab and Rituximab in Active Multiple Sclerosis*.2020. URL: https://clinicaltrials.gov/ct2/show/NCT04688788 (Accessed 8 May 2024).	Comparator not informative to the network
Ozakbas S, Cinar B, Kosehasanogullari G, Kahraman T, Oz D, Kursun B. Monthly methylprednisolone in combination with interferon beta or glatiramer acetate for relapsing-remitting multiple sclerosis: A multicentre, single-blind, prospective trial. Clinical neurology and neurosurgery. 2017;160:69-72. doi:10.1016/j.clineuro.2017.06.016.	Did not evaluate intervention of interest
Pakdaman H, Abbasi M, Gharagozli K, Ashrafi F, Delavar Kasmaei H, Amini Harandi A. A randomized double-blind trial of comparative efficacy and safety of Avonex and CinnoVex for treatment of relapsing-remitting multiple sclerosis. Neurological sciences : official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology. 2018;39(12):2107-2113. doi:10.1007/s10072-018-3550-8.	Not informative to the network - compares brands
Panitch H, Miller A, Paty D, Weinshenker B. Interferon beta-1b in secondary progressive MS: results from a 3-year controlled study. Neurology. 2004;63(10):1788-95. doi:10.1212/01.wnl.0000146958.77317.3e.	MS but not >90% RRMS
Pantzaris M, Bakirtzis C, Grigoriadis N, et al. Phase III, randomised, double-blind, placebo-controlled trial of Neuroaspis plp10 as an adjuvant treatment for relapsing multiple sclerosis: the MINERAL Study. BMJ neurology open. 2022;4(2):e000334. doi:10.1136/bmjno-2022-000334.	Not informative to the network - non DMT add on
Patti F, Amato M, Filippi M, Gallo P, Trojano M, Comi G. A double blind, placebo-controlled, phase II, add-on study of cyclophosphamide (CTX) for 24 months in patients affected by multiple sclerosis on a background therapy with interferon-beta study denomination: CYCLIN. Journal of the neurological sciences. 2004;223(1):69-71. doi:10.1016/j.jns.2004.04.023.	Not informative to the network - non DMT add on

Citation	Reason for exclusion
Patti F, L'Episcopo M, Cataldi M, Reggio A. Natural interferon-beta treatment of relapsing-remitting and secondary-progressive multiple sclerosis patients. A two-year study. Acta neurologica Scandinavica. 1999;100(5):283-9. doi:10.1111/j.1600-0404.1999.tb00397.x.	Did not evaluate intervention of interest
2009-012716-40. *The Effect of the Dose of PI-2301 on Efficacy, Safety, and Tolerability, in Subjects with the Relapsing Remitting Form of Multiple Sclerosis: A Phase 2 Randomized, double-blind, four–arm, parallel, placebo-controlled and active descriptive-comparator, 40 week trial*.2009. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2009-012716-40 (Accessed 8 May 2024).	RRMS but not in adults
Petracca M, Quarantelli M, Moccia M, et al. ProspeCtive study to evaluate efficacy, safety and tOlerability of dietary supplemeNT of Curcumin (BCM95) in subjects with Active relapsing MultIple Sclerosis treated with subcutaNeous Interferon beta 1a 44 mcg TIW (CONTAIN): A randomized, controlled trial. Multiple sclerosis and related disorders. 2021;56:103274. doi:10.1016/j.msard.2021.103274.	Not informative to the network - non DMT add on
Polman C, Barkhof F, Kappos L, et al. Oral interferon beta-1a in relapsing-remitting multiple sclerosis: a double-blind randomized study. Multiple sclerosis (Houndmills, Basingstoke, England). 2003;9(4):342-8. doi:10.1191/1352458503ms923oa.	Did not evaluate intervention of interest - drug is of interest but in different presentation/dose than licensed
Popova E, Boiko A, Boiko O, et al. Results of a Randomized Open Multicenter Comparative Study of the Tolerability and Safety of Gilenya (fingolimod) in Patients with Remitting Multiple Sclerosis (the GIMN study). Neuroscience and Behavioral Physiology. 2016;:1-5. doi:10.1007/s11055-016-0370-2.	Not informative to the network - drug of interest but not in a licensed dose
Popova E, Boiko A, Vasil'ev A, et al. [Results of a comparative clinical trial of the Russian Beta - interferon-1b bioanalogue (infibeta)]. Zhurnal nevrologii i psikhiatrii imeni S.S. Korsakova. 2012;112(5):56-61.	Not informative to the network - compares brands
Pozzilli C, De Giglio L, Barletta V, et al. Oral contraceptives combined with interferon beta in multiple sclerosis. Neurology(R) neuroimmunology & neuroinflammation. 2015;2(4):e120. doi:10.1212/nxi.0000000000000120.	Not informative to the network - non DMT add on
Pozzilli C, Millefiorini E, Bastianello S, et al. Recombinant interferon beta 1a in the treatment of relapsing-remitting multiple sclerosis. Nuova Rivista di Neurologia. 1995;5(6 SUPPL. 1):5-9.	Can't locate
Radue E, Stuart W, Calabresi P, et al. Natalizumab plus interferon beta-1a reduces lesion formation in relapsing multiple sclerosis. Journal of the neurological sciences. 2010;292(1-2):28-35. doi:10.1016/j.jns.2010.02.012.	Comparator not informative to the network
Ravnborg M, Sorensen P, Andersson M, et al. Methylprednisolone in combination with interferon beta-1a for relapsing-remitting multiple sclerosis (MECOMBIN study): a multicentre, double-blind, randomised, placebo-controlled, parallel-group trial. The Lancet. Neurology. 2010;9(7):672-80. doi:10.1016/s1474-4422(10)70132-0.	Not informative to the network - non DMT add on
ISRCTN31557558. *A pilot multi-centre randomised controlled trial of sequential treatment with Mitoxantrone and Glatiramer Acetate vs Interferon Beta-1a in early active relapsing remitting Multiple Sclerosis*.2005. URL: http://isrctn.com/ISRCTN31557558 (Accessed 8 May 2024).	Comparator not informative to the network

Citation	Reason for exclusion
Remington G, Treadaway K, Frohman T, et al. A one-year prospective, randomized, placebo-controlled, quadruple-blinded, phase II safety pilot trial of combination therapy with interferon beta-1a and mycophenolate mofetil in early relapsing-remitting multiple sclerosis (TIME MS). Therapeutic advances in neurological disorders. 2010;3(1):3-13. doi:10.1177/1756285609355851.	Not informative to the network - non DMT add on
NCT05758831. *RItuximab Versus Ocrelizumab in Relapsing-remitting Multiple Sclerosis*.2023. URL: https://clinicaltrials.gov/ct2/show/NCT05758831 (Accessed 8 May 2024).	Did not evaluate intervention of interest
rct20150628022956N. *The effect of salimarin in patients with multiple sclerosis*.2019. URL: http://en.irct.ir/trial/35513 (Accessed 8 May 2024).	Not informative to the network - non DMT add on
Rinaldi F, Perini P, Atzori M, Favaretto A, Seppi D, Gallo P. Disease-modifying drugs reduce cortical lesion accumulation and atrophy progression in relapsing-remitting multiple sclerosis: results from a 48-month extension study. Multiple sclerosis international. 2015;2015:369348. doi:10.1155/2015/369348.	Extension/expansion study
Rivera V. [The treatment of multiple sclerosis with beta-interferon 1a]. Tratamiento de la esclerosis multiple con interferon-beta 1a. 2000;31(5):470-1.	MS but not >90% RRMS
Romano S, Ferraldeschi M, Bagnato F, et al. Drug Holiday of Interferon Beta 1b in Multiple Sclerosis: A Pilot, Randomized, Single Blind Study of Non-inferiority. Frontiers in neurology. 2019;10:695. doi:10.3389/fneur.2019.00695.	Not informative to the network - compares different protocols
Romine J, Sipe J, Koziol J, Zyroff J, Beutler E. A double-blind, placebo-controlled, randomized trial of cladribine in relapsing-remitting multiple sclerosis. Proceedings of the Association of American Physicians. 1999;111(1):35-44. doi:10.1046/j.1525-1381.1999.09115.x.	Did not evaluate intervention of interest - drug is of interest but in different presentation/dose than licensed
Rovaris M, Comi G, Ladkani D, Wolinsky J, Filippi M. Short-term correlations between clinical and MR imaging findings in relapsing-remitting multiple sclerosis. AJNR. American journal of neuroradiology. 2003;24(1):75-81.	Not a RCT
Rovaris M, Comi G, Rocca M, et al. Long-term follow-up of patients treated with glatiramer acetate: a multicentre, multinational extension of the European/Canadian double-blind, placebo-controlled, MRI-monitored trial. Multiple sclerosis (Houndmills, Basingstoke, England). 2007;13(4):502-8. doi:10.1177/1352458506070704.	Not a RCT
Rudick R, Cookfair D, Simonian N, et al. Cerebrospinal fluid abnormalities in a phase III trial of Avonex (IFNbeta-1a) for relapsing multiple sclerosis. Journal of Neuroimmunology. 1999;93(1-2):8-14. doi:10.1016/s0165-5728(98)00174-x.	Does not report on one of the outcomes of interest
Rudick R, Stuart W, Calabresi P, et al. Natalizumab plus interferon beta-1a for relapsing multiple sclerosis. The New England journal of medicine. 2006;354(9):911-23. doi:10.1056/nejmoa044396.	Comparator not informative to the network
Ryerson L, Foley J, Defer G, et al. Exploratory clinical efficacy and patient-reported outcomes from NOVA: A randomized controlled study of intravenous natalizumab 6-week dosing versus continued 4-week dosing for relapsing-remitting multiple sclerosis. Multiple sclerosis and related disorders. 2023;72:104561. doi:10.1016/j.msard.2023.104561.	Not informative to the network - compares different protocols

Citation	Reason for exclusion
Saida T, Itoyama Y, Kikuchi S, et al. Long-term efficacy and safety of fingolimod in Japanese patients with relapsing multiple sclerosis: 3-year results of the phase 2 extension study. BMC neurology. 2017;17(1):17. doi:10.1186/s12883-017-0794-5.	Extension/expansion study
Saida T, Kira J, Kishida S, et al. Safety and Efficacy of Natalizumab in Japanese Patients with Relapsing-Remitting Multiple Sclerosis: Open-Label Extension Study of a Phase 2 Trial. Neurology and therapy. 2017;6(1):39-55. doi:10.1007/s40120-016-0059-z.	Extension/expansion study
Saida T, Kira J, Ueno Y, Harada N, Hirakata T. Long-term efficacy and safety of intramuscular interferon beta-1a: Randomized postmarketing trial of two dosing regimens in Japanese patients with relapsing-remitting multiple sclerosis. Multiple sclerosis and related disorders. 2016;7:102-8. doi:10.1016/j.msard.2016.02.002.	Not informative to the network - compares different protocols
Saida T, Tashiro K, Itoyama Y, Sato T, Ohashi Y, Zhao Z. Interferon beta-1b is effective in Japanese RRMS patients: a randomized, multicenter study. Neurology. 2005;64(4):621-30. doi:10.1212/01.wnl.0000151856.10387.e2.	Not informative to the network - drug of interest but not in a licensed dose
Saida T, Yamamura T, Kondo T, et al. A randomized placebo-controlled trial of delayed-release dimethyl fumarate in patients with relapsing-remitting multiple sclerosis from East Asia and other countries. BMC Neurology. 2019;19(1):5. doi:10.1186/s12883-018-1220-3.	Did not evaluate intervention of interest
Sandberg-Wollheim M, Hommes O, Hughes R, Paty D, Abdul-Ahad A. Recombinant human interferon beta in the treatment of relapsing-remitting and secondary progressive multiple sclerosis. Multiple sclerosis (Houndmills, Basingstoke, England). 1995;1 Suppl 1:S48-50.	Can't locate
49585. *A Multi-center, Open-label, Single-arm, Before and After Switch Study to Evaluate the Efficacy, Safety and Tolerability of Alemtuzumab in Pediatric Patients with Relapsing Remitting Multiple Sclerosis (RRMS) with Disease Activity on Prior Disease Modifying Therapy (DMT)*.2019. URL: https://onderzoekmetmensen.nl/en/trial/49585 (Accessed 8 May 2024).	Not a RCT
2006-005270-47. *International, multicenter, Phase IIIb study of subcutaneous every-other-day treatment of patients with relapsing multiple sclerosis with (Phase A) double-blind Betaseron/Betaferon 250 µg or 500 µg or open-label Betaseron/Betaferon 250 µg and (Phase B) open-label Betaseron/Betaferon 500 µg version: final internal approved - Beyond Follow-up*.2006. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2006-005270-47 (Accessed 8 May 2024).	Not informative to the network - drug of interest but not in a licensed dose
Selmaj K, Barkhof F, Belova A, et al. Switching from branded to generic glatiramer acetate: 15-month GATE trial extension results. Multiple sclerosis (Houndmills, Basingstoke, England). 2017;23(14):1909-1917. doi:10.1177/1352458516688956.	Extension/expansion study
Ctri 3897. *Study to evaluate the safety and efficacy of NU100 in patients with relapsing forms of multiple sclerosis*.2012. URL: http://www.ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=3897 (Accessed 8 May 2024).	Can't locate
2005-001026-89. *Phase IV, multicenter, open label, randomized study of Rebif® 44 mcg administered three times per week by subcutaneous injection compared with no treatment in the therapy of relapsing multiple sclerosis after mitoxantrone - Deescalation to Rebif® after Mitoxantrone therapy (REMAIN study)*.2005. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2005-001026-89 (Accessed 8 May 2024).	Not informative to the network - non DMT add on

Citation	Reason for exclusion
Shaygannezhad V, Amini H. Comparing the efficacy of monthly cyclophosphamide as monotherapy versus daily fingolimod in relapsing remitting and secondary progressive multiple sclerosis. Journal of Isfahan Medical School. 2017;35(435):719-725.	Comparator not informative to the network
ISRCTN88667898. *Autologous stem cell transplantation versus alemtuzumab, ocrelizumab, ofatumumab or cladribine in relapsing-remitting multiple sclerosis*.2020. URL: https://www.isrctn.com/ISRCTN88667898 (Accessed 8 May 2024).	Comparator not informative to the network
NCT03133403. *Hematopoietic Stem Cell Therapy for Inflammatory Multiple Sclerosis Failing Alternate Approved Therapy*.2016. URL: https://clinicaltrials.gov/show/NCT03133403 (Accessed 8 May 2024).	Does not report on one of the outcomes of interest
Sibley W. Clinical efficacy of interferon beta-1b in multiple sclerosis: The US/Canadian multicentre trial evidence. Clinical Immunotherapeutics. 1996;5(SUPPL. 1):41-46.	Not a primary study
Sibley W. Interferon beta-1b in the treatment of multiple sclerosis: Final outcome of the randomized controlled trial. Neurology. 1995;45(7):1277-1285.	Extension/expansion study
Siger-Zajdel M, Lewanska M, Zaleski K, et al. [Open trial of the effectiveness of interferon beta 1a (Avonex) in the treatment of multiple sclerosis in Poland: MRI results]. Badanie otwarte oceny skutecznosci dzialania interferonu beta 1A (Avonexu) w leczeniu stwardnienia rozsianego w Polsce. Wyniki analizy badania rezonansu magnetycznego. 2003;37(6):1185-97.	Can't locate
Simaniv T, Zakharova M, Boyko A, et al. Safety aspects without loss of effectiveness in the switch of patients with multiple sclerosis from the original drug glatiramer acetate copaxone-teva on the biosimilar timexon. Russian Neurological Journal. 2019;(4):44-51. doi:10.30629/2658-7947-2019-24-4-44-51.	Not informative to the network - compares brands
Singer B, Bandari D, Cascione M, et al. Comparative injection-site pain and tolerability of subcutaneous serum-free formulation of interferonbeta-1a versus subcutaneous interferonbeta-1b: results of the randomized, multicenter, Phase IIIb REFORMS study. BMC neurology. 2012;12:154. doi:10.1186/1471-2377-12-154.	Does not report on one of the outcomes of interest
Soilu-Hanninen M, Aivo J, Lindstrom B, et al. A randomised, double blind, placebo controlled trial with vitamin D3 as an add on treatment to interferon beta-1b in patients with multiple sclerosis. Journal of neurology, neurosurgery, and psychiatry. 2012;83(5):565-71. doi:10.1136/jnnp-2011-301876.	Not informative to the network - non DMT add on
Sorensen P, Lisby S, Grove R, et al. Safety and efficacy of ofatumumab in relapsing-remitting multiple sclerosis: a phase 2 study. Neurology. 2014;82(7):573-81. doi:10.1212/wnl.0000000000000125.	Did not evaluate intervention of interest - drug is of interest but in different presentation/dose than licensed
Sorensen P, Lycke J, Eralinna J, et al. Simvastatin as add-on therapy to interferon beta-1a for relapsing-remitting multiple sclerosis (SIMCOMBIN study): a placebo-controlled randomised phase 4 trial. The Lancet. Neurology. 2011;10(8):691-701. doi:10.1016/s1474-4422(11)70144-2.	Not informative to the network - non DMT add on
Sorensen P, Mellgren S, Svenningsson A, et al. NORdic trial of oral Methylprednisolone as add-on therapy to Interferon beta-1a for treatment of relapsing-remitting Multiple Sclerosis (NORMIMS study): a randomised, placebo-controlled trial. The Lancet. Neurology. 2009;8(6):519-29. doi:10.1016/s1474-4422(09)70085-7.	Not informative to the network - non DMT add on

Citation	Reason for exclusion
Sorensen P, Sellebjerg F, Lycke J, et al. Minocycline added to subcutaneous interferon beta-1a in multiple sclerosis: randomized RECYCLINE study. European journal of neurology. 2016;23(5):861-70. doi:10.1111/ene.12953.	Not informative to the network - non DMT add on
Steingo B, Al Malik Y, Bass A, et al. Long-term efficacy and safety of alemtuzumab in patients with RRMS: 12-year follow-up of CAMMS223. Journal of neurology. 2020;267(11):3343-3353. doi:10.1007/s00415-020-09983-1.	Extension/expansion study
Stelmasiak Z, Solski J, Nowicki J, Jakubowska B, Ryba M, Grieb P. Effect of parenteral cladribine on relapse rates in patients with relapsing forms of multiple sclerosis: results of a 2-year, double-blind, placebo-controlled, crossover study. Multiple sclerosis (Houndmills, Basingstoke, England). 2009;15(6):767-70. doi:10.1177/1352458509103610.	MS but not >90% RRMS
Stepien A, Chalimoniuk M, Lubina-Dabrowska N, Chrapusta S, Galbo H, Langfort J. Effects of interferon beta-1a and interferon beta-1b monotherapies on selected serum cytokines and nitrite levels in patients with relapsing-remitting multiple sclerosis: a 3-year longitudinal study. Neuroimmunomodulation. 2013;20(4):213-22. doi:10.1159/000348701.	Not a RCT
NCT05834855. *Non-inferiority Study of Rituximab Compared to Ocrelizumab in Relapsing MS*.2023. URL: https://clinicaltrials.gov/show/NCT05834855 (Accessed 8 May 2024).	Did not evaluate intervention of interest
jRCT2031210175. *Protocol Number; COMB157G1401*.2021. URL: https://jrct.niph.go.jp/latest-detail/jRCT2031210175 (Accessed 8 May 2024).	Extension/expansion study
Svenningsson A, Frisell T, Burman J, et al. Safety and efficacy of rituximab versus dimethyl fumarate in patients with relapsing-remitting multiple sclerosis or clinically isolated syndrome in Sweden: a rater-blinded, phase 3, randomised controlled trial. The Lancet. Neurology. 2022;21(8):693-703. doi:10.1016/s1474-4422(22)00209-5.	Did not evaluate intervention of interest
2011-000888-27. *A clinical trial comparing the efficacy, and safety and tolerability of two disease modifying MS drugs (GTR and Copaxone®) in patients with relapsing remitting multiple sclerosis for 9 months followed by a 15 month GTR treatment part to evaluate efficacy and safety of long-term GTR treatment*.2011. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2011-000888-27 (Accessed 8 May 2024).	Not informative to the network - compares brands
2013-002082-19. *A clinical study in subjects with relapsing-remitting multiple sclerosis (RRMS) to assess the efficacy, safety and tolerability of two oral doses of laquinimod either of 0.6 mg/day or 1.2mg/day (experimental drug) as compared to Interferon ß-1a (Avonex, authorised drug) administered once weekly*.2013. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2013-002082-19 (Accessed 8 May 2024).	Comparator not informative to the network
2006-002037-20. *A multi-national, multi-centre, randomized, parallel-group, double-blind study to compare the efficacy, tolerability and safety of Glatiramer Acetate Injection 40 mg/ml to that of Glatiramer Acetate Injection 20 mg/ml administered once daily by subcutaneous injection in subjects with relapsing remitting (RR) Multiple Sclerosis (MS) - FORTE*.2006. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2006-002037-20 (Accessed 8 May 2024).	Not informative to the network - compares different protocols
2011-005550-57. *A clinical study in patients with multiple sclerosis to assess the efficacy, safety and tolerability of Glatiramer Acetate (GA) 20 mg/0.5 ml (experimental drug)*.2012. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2011-005550-57 (Accessed 8 May 2024).	Terminated study

Citation	Reason for exclusion
Togha M, Karvigh S, Nabavi M, et al. Simvastatin treatment in patients with relapsing-remitting multiple sclerosis receiving interferon beta 1a: a double-blind randomized controlled trial. Multiple sclerosis (Houndmills, Basingstoke, England). 2010;16(7):848-54. doi:10.1177/1352458510369147.	Not informative to the network - non DMT add on
Toghianifar N, Ashtari F, Zarkesh-Esfahani S, Mansourian M. Effect of high dose vitamin D intake on interleukin-17 levels in multiple sclerosis: a randomized, double-blind, placebo-controlled clinical trial. Journal of neuroimmunology. 2015;285:125-8. doi:10.1016/j.jneuroim.2015.05.022.	Not informative to the network - non DMT add on
Toorop A, van Lierop Z, Gelissen L, et al. Prospective trial of natalizumab personalised extended interval dosing by therapeutic drug monitoring in relapsing-remitting multiple sclerosis (NEXT-MS). Journal of neurology, neurosurgery, and psychiatry. 2024;95(5):392-400. doi:10.1136/jnnp-2023-332119.	Not a primary study
Tremlett H. Randomized multicenter trial of natalizumab in acute MS relapses: clinical and MRI effects. Neurology. 2005;64(1):174-5. doi:10.1212/wnl.64.1.174.	Not a primary study
Trojano M, Ramio-Torrenta L, Grimaldi L, et al. A randomized study of natalizumab dosing regimens for relapsing-remitting multiple sclerosis. Multiple sclerosis (Houndmills, Basingstoke, England). 2021;27(14):2240-2253. doi:10.1177/13524585211003020.	Did not evaluate intervention of interest
2006-004937-13. *multicentee randomized controlled study of azathioprine versus iterferon beta in relapsing remitting multiple sclerosis - M.A.I.N. trial*.2007. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2006-004937-13 (Accessed 8 May 2024).	Not a primary study
2017-005129-18. *Clinical trial to evaluate the effectiveness and safety of IFN beta-1a (IFN beta-1a), injected once a week via intramuscolar (i.m.), and glatiramer-acetate (GA) in children/adolescent patients with multiple sclerosis*.2018. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2017-005129-18 (Accessed 8 May 2024).	RRMS but not in adults
2014-000709-10. *Investigation on how alemtuzumab acts in patients with relapsing remitting multiple sclerosis*.2014. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2014-000709-10 (Accessed 8 May 2024).	Not a RCT
NCT04578639. *Ocrelizumab VErsus Rituximab Off-Label at the Onset of Relapsing MS Disease*.2020. URL: https://clinicaltrials.gov/ct2/show/NCT04578639 (Accessed 8 May 2024).	Did not evaluate intervention of interest
2016-001166-29. *A randomised controlled trial to compare ocrelizumab or alemtuzumab with autologous hematopoietic stem cell transplantation (aHSCT) in high inflammatory multiple sclerosis (COAST)*.2019. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2016-001166-29 (Accessed 8 May 2024).	Terminated study
2013-002378-26. *Switch To RItuXimab in MS extension An extension study of an ongoing clinical trial where people with multiple sclerosis switch therapy from interferon or glatiramere injections to rituximab, a monoclonal antibody that eliminate B lymphocytes*.2013. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2013-002378-26 (Accessed 8 May 2024).	Did not evaluate intervention of interest

Citation	Reason for exclusion
Valenzuela B, Olsson Gisleskog P, Poggesi I, et al. An exposure-response analysis of ponesimod clinical efficacy in a randomized phase III study in patients with relapsing multiple sclerosis. CPT: pharmacometrics & systems pharmacology. 2022;11(10):1294-1304. doi:10.1002/psp4.12778.	Does not report on one of the outcomes of interest
Van Wijmeersch B, Singer B, Boster A, et al. Efficacy of alemtuzumab over 6 years in relapsing-remitting multiple sclerosis patients who relapsed between courses 1 and 2: Post hoc analysis of the CARE-MS studies. Multiple Sclerosis Journal. 2020;26(13):1719-1728. doi:10.1177/1352458519881759.	Extension/expansion study
Vermersch P, Czlonkowska A, Grimaldi L, et al. Teriflunomide versus subcutaneous interferon beta-1a in patients with relapsing multiple sclerosis: a randomised, controlled phase 3 trial. Multiple sclerosis (Houndmills, Basingstoke, England). 2014;20(6):705-16. doi:10.1177/1352458513507821.	Comparator not informative to the network
Vermersch P, Scaramozza M, Levin S, et al. Effect of Dimethyl Fumarate vs Interferon beta-1a in Patients With Pediatric-Onset Multiple Sclerosis: The CONNECT Randomized Clinical Trial. JAMA network open. 2022;5(9):e2230439. doi:10.1001/jamanetworkopen.2022.30439.	MS but not >90% RRMS
Irct201705108323N. *Evaluating the efficacy and side effects fingolimod in 3 -year follow-up of patients with recurrent forms of multiple sclerosis*.2017. URL: http://en.irct.ir/trial/8804 (Accessed 8 May 2024).	Not a RCT
Irct201112267419N. *Randomized, open labeled, multicenter study evaluating safety Fingolide® in patients with Relapsing-Remitting Multiple Sclerosis*.2012. URL: http://en.irct.ir/trial/7881 (Accessed 8 May 2024).	Not a RCT
Irct201406018323N. *The evaluation of the efficacy and safety of oral fingolimod in relapsing remitting multiple sclerosis*.2015. URL: http://en.irct.ir/trial/8799 (Accessed 8 May 2024).	Not a RCT
Vollmer T, Cohen J, Alvarez E, et al. Safety results of administering ocrelizumab per a shorter infusion protocol in patients with primary progressive and relapsing multiple sclerosis. Multiple sclerosis and related disorders. 2020;46:102454. doi:10.1016/j.msard.2020.102454.	Comparator not informative to the network
Vollmer T, Panitch H, Bar-Or A, et al. Glatiramer acetate after induction therapy with mitoxantrone in relapsing multiple sclerosis. Multiple sclerosis (Houndmills, Basingstoke, England). 2008;14(5):663-70. doi:10.1177/1352458507085759.	Did not evaluate intervention of interest
Vollmer T, Sorensen P, Selmaj K, et al. A randomized placebo-controlled phase III trial of oral laquinimod for multiple sclerosis. Journal of neurology. 2014;261(4):773-83. doi:10.1007/s00415-014-7264-4.	Comparator not informative to the network
Voskuhl R, Wang H, Wu T, et al. Estriol combined with glatiramer acetate for women with relapsing-remitting multiple sclerosis: a randomised, placebo-controlled, phase 2 trial. The Lancet. Neurology. 2016;15(1):35-46. doi:10.1016/s1474-4422(15)00322-1.	Not informative to the network - non DMT add on
NCT04458688. *Investigating the Effect of Ocrelizumab in African Americans and Caucasians With Relapsing Multiple Sclerosis*.2020. URL: https://clinicaltrials.gov/show/NCT04458688 (Accessed 8 May 2024).	Not a RCT

Citation	Reason for exclusion
Wolinsky J, Borresen T, Dietrich D, et al. GLACIER: An open-label, randomized, multicenter study to assess the safety and tolerability of glatiramer acetate 40 mg three-times weekly versus 20 mg daily in patients with relapsing-remitting multiple sclerosis. Multiple sclerosis and related disorders. 2015;4(4):370-6. doi:10.1016/j.msard.2015.06.005.	Did not evaluate intervention of interest
Wray S, Then Bergh F, Wundes A, et al. Efficacy and Safety Outcomes with Diroximel Fumarate After Switching from Prior Therapies or Continuing on DRF: Results from the Phase 3 EVOLVE-MS-1 Study. Advances in therapy. 2022;39(4):1810-1831. doi:10.1007/s12325-022-02068-7.	Did not evaluate intervention of interest
Wroe S. Effects of dose titration on tolerability and efficacy of interferon beta-1b in people with multiple sclerosis. The Journal of international medical research. 2005;33(3):309-18. doi:10.1177/147323000503300306.	Not informative to the network - compares different protocols
Wynn D, Kaufman M, Montalban X, et al. Daclizumab in active relapsing multiple sclerosis (CHOICE study): a phase 2, randomised, double-blind, placebo-controlled, add-on trial with interferon beta. The Lancet. Neurology. 2010;9(4):381-90. doi:10.1016/s1474-4422(10)70033-8.	Not informative to the network - non DMT add on
Wynn D, Meyer C, Allen N, O'Brien D. Optimal dosing of immunomodulating drugs: A dose-comparison study of GA in RRMS. Progress in Neurotherapeutics and Neuropsychopharmacology. 2008;3(1):137-151. doi:10.1017/s1748232107000110.	Not informative to the network - drug of interest but not in a licensed dose
2012-003735-32. *Study to compare the efficacy and/or safety of masitinib to interferon beta-1a, interferon beta-1b, peginterferon beta-1a or glatiramer acetate in patients with relapsing remitting multiple sclerosis with unsatisfactory response to these first line treatments*.2015. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2012-003735-32 (Accessed 8 May 2024).	Terminated study
2021-005746-15. *A Rollover Study to Evaluate the Long-Term Safety and Efficacy of Ocrelizumab In Patients with Multiple Sclerosis*.2022. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2021-005746-15 (Accessed 8 May 2024).	Not a RCT
2020-004128-41. *A Study to Evaluate Safety and Efficacy of Ocrelizumab in Comparison with Fingolimod in Children and Adolescents with Relapsing-Remitting Multiple Sclerosis*.2021. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2020-004128-41 (Accessed 8 May 2024).	RRMS but not in adults
2015-005597-38. *A Study to Evaluate the Efficacy and Safety of Ocrelizumab in Patients With Relapsing Remitting Multiple Sclerosis*.2016. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2015-005597-38 (Accessed 8 May 2024).	Not an RCT
2020-000893-69. *A Study to Evaluate the Efficacy, Safety and Pharmacokinetics of a Higher Dose of Ocrelizumab in Adults with Relapsing Multiple Sclerosis*.2020. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2020-000893-69 (Accessed 8 May 2024).	Not informative to the network - compares different protocols

Citation	Reason for exclusion
32113. *A Phase IIIB, Double Blind, Placebo-Controlled, Multcenter, Parallel Group, Extension Trial to Evaluate the Safety and Tolerability of Oral Cladribine in Subjects with Relapsing-Remitting Multiple Sclerosis Who Have Completed Trial 25643 (Clarity)*.2008. URL: https://onderzoekmetmensen.nl/en/trial/32113 (Accessed 8 May 2024).	Extension/expansion study
2010-024017-31. *A 6-month, Randomized, Active Comparator, Open-label, Multi-Center Study to Evaluate Patient OutComes, Safety and Tolerability of Fingolimod (FTY720) 0.5 mg/day in Patients with Relapsing Remitting Multiple Sclerosis who are candidates for MS therapy change from Previous Disease Modifying Therapy - GOLDEN*.2011. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2010-024017-31 (Accessed 8 May 2024).	Comparator not informative to the network
2014-001012-19. *Effects of fingolimod on advanced brain measures and clinical measures in multiple sclerosis*.2014. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2014-001012-19 (Accessed 8 May 2024).	Not a RCT
Zarbin M, Jampol L, Jager R, et al. Ophthalmic evaluations in clinical studies of fingolimod (FTY720) in multiple sclerosis. Ophthalmology. 2013;120(7):1432-9. doi:10.1016/j.ophtha.2012.12.040.	Extension/expansion study
Zavalishin I, Gusev E, Iakhno N, et al. [Results of a multicenter study of Rebif-22 mcg administration in Russia]. Rezul'taty multitsentrovogo issledovaniia effektivnosti preparata Rebif-22 mkg v Rossii. 2003;(Spec No 2):73-8.	Not a RCT
Zecca C, Riccitelli G, Calabrese P, et al. Treatment satisfaction, adherence and behavioral assessment in patients de-escalating from natalizumab to interferon beta. BMC neurology. 2014;14:38. doi:10.1186/1471-2377-14-38.	Did not evaluate intervention of interest
Ziemssen T, Bass A, Berkovich R, et al. Efficacy and Safety of Alemtuzumab Through 9 Years of Follow-up in Patients with Highly Active Disease: Post Hoc Analysis of CARE-MS I and II Patients in the TOPAZ Extension Study. CNS drugs. 2020;34(9):973-988. doi:10.1007/s40263-020-00749-x.	Extension/expansion study
Zimmermann C, Walther E, Goebels N, et al. [Interferon beta-1b for treatment of secondary chronic progressive multiple sclerosis]. Interferon beta-1b zur Behandlung der sekundar chronisch progredienten multiplen Sklerose. 1999;70(8):759-63. doi:10.1007/s001150050508.	MS but not >90% RRMS

Studies excluded at full-text screening (Review of Cost-effectiveness)

Table 42 Studies excluded at full-text screening (Review of Cost-effectiveness)

Citation	Reason for exclusion
Ahmad H, Campbell JA, van der Mei I, Taylor BV, Xia Q, Zhao T, et al. Estimating the disutility of relapse in relapsing-remitting and secondary progressive multiple sclerosis using the EQ-5D-5L, AQoL-8D, EQ-5D-5L-psychosocial, and SF-6D: implications for health economic evaluation models. Quality of Life Research 2023;32(12):	Exclude not an economic evaluation
Ahmad H, van der Mei I, Taylor B, Zhao T, Xia Q, Palmer AJ. Does health-related quality of life differ between people with relapse onset and progressive onset Multiple Sclerosis? Multiple Sclerosis and Related Disorders 2021;54	Exclude QoL
Alasdair Millar J. The cost of teriflunomide in the treatment of relapsing remitting multiple sclerosis. New Zealand Medical Journal 2019;132	Exclude RRMS New Zealand
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Citation	Reason for exclusion
Su W, Kansal A, Vicente C, Deniz B, Sarda S. The cost-effectiveness of delayed-release dimethyl fumarate for the treatment of relapsing-remitting multiple sclerosis in Canada. *Journal of Medical Economics* 2016;**19**(7):	Exclude RRMS Canada
Svensson M, Fajutrao L. Costs of formal and informal home care and quality of life for patients with multiple sclerosis in sweden. *Multiple Sclerosis International* 2014;**2014**	Exclude MS Sweden
Taheri S, Sahraian MA, Yousefi N. Cost-effectiveness of alemtuzumab and natalizumab for relapsing-remitting multiple sclerosis treatment in Iran: decision analysis based on an indirect comparison. *Journal of Medical Economics* 2019;**22**(1):	Exclude RRMS Iran
Tappenden P, Saccardi R, Confavreux C, Sharrack B, Muraro PA, Mancardi GL*, et al.* Autologous haematopoietic stem cell transplantation for secondary progressive multiple sclerosis: an exploratory cost-effectiveness analysis. *Bone marrow transplantation* 2010;**45**(6): 1014-1021	Exclude SPMS UK
Torabipour A, Asl ZA, Majdinasab N, Ghasemzadeh R, Tabesh H, Arab M. A study on the direct and indirect costs of multiple sclerosis based on expanded disability status scale score in khuzestan, iran. *International Journal of Preventive Medicine* 2014;**5**(9):	Exclude MS Iran
Tosh J, Dixon S, Carter A, Daley A, Petty J, Roalfe A*, et al.* Cost effectiveness of a pragmatic exercise intervention (EXIMS) for people with multiple sclerosis: economic evaluation of a randomised controlled trial. *Multiple Sclerosis* 2014;**20**(8):	Exclude intervention
Touchette DR, Durgin TL, Wanke LA, Goodkin DE. A cost-utility analysis of mitoxantrone hydrochloride and interferon beta-1b in the treatment of patients with secondary progressive or progressive relapsing multiple sclerosis. *Clinical Therapeutics* 2003;**25**(2): 611-634	Exclude SPMS US
van Eijndhoven E, Brauer M, Kee R, MacEwan J, Mucha L, Wong SL*, et al.* Modeling the impact of patient treatment preference on health outcomes in relapsing-remitting multiple sclerosis. *Journal of medical economics* 2020;**23**(5): 474-483	Exclude Intervention
van Mastrigt GA, Evers SM, Heerings M, Visser LH, Ruimschotel RP, Hussaarts A*, et al.* An economic evaluation attached to a single-centre, parallel group, unmasked, randomized controlled trial of a 3-day intensive social cognitive treatment (can do treatment) in patients with relapsing remitting multiple sclerosis and low disability. *Journal of Medical Economics* 2019;**22**(10):	Exclude RRMS Netherlands
Vandhuick O, Payet M, Preaud E, Lortet-Tieulent J, Raguideau F, Chevreuil O*, et al.* Economic burden of highly active relapsing-remitting multiple sclerosis patients in the French national health insurance database. *Expert Review of Pharmacoeconomics & Outcomes Research* 2021;**21**(5):	Exclude RRMS France
Veauthier C, Hasselmann H, Gold SM, Paul F. The Berlin Treatment Algorithm: recommendations for tailored innovative therapeutic strategies for multiple sclerosis-related fatigue. *The EPMA Journal* 2016;**7**	Exclude not an economic evaluation
Versteegh MM, Huygens SA, Wokke BWH, Smolders J. Effectiveness and Cost-Effectiveness of 360 Disease-Modifying Treatment Escalation Sequences in Multiple Sclerosis. *Value in Health* 2022;**25**(6): 984-991	Exclude RRMS Netherlands
Viktor Chirikov, Ingrid Ma, Namita Joshi, Dipen Patel, Alden Smith, Cindy Giambrone, et al. Cost-Effectiveness of Alemtuzumab in the Treatment of Relapsing Forms of Multiple Sclerosis in the United States. Value in Health 2019;22(6):	Exclude RRMS US
Visser LA, Folcher M, Delgado Simao C, Gutierrez Arechederra B, Escudero E, Uyl-de Groot CA*, et al.* The Potential Cost-Effectiveness of a Cell-Based Bioelectronic Implantable Device Delivering Interferon-beta1a Therapy Versus Injectable Interferon-beta1a Treatment in Relapsing-Remitting Multiple Sclerosis. *PharmacoEconomics* 2022;**40**(1):	Exclude RRMS Netherlands
Walker A, Watson C, Alexopoulos ST, Deniz B, Arnold R, Bates D. A benefit-risk analysis of natalizumab in the treatment of patients with multiple sclerosis when considering the risk of progressive multifocal leukoencephalopathy. *Current Medical Research & Opinion* 2014;**30**(4):	Exclude RRMS Austria
Walter E, Berger T, Bajer-Kornek B, Deisenhammer F. Cost-utility analysis of alemtuzumab in comparison with interferon beta, fingolimod, and natalizumab treatment for relapsing-remitting multiple sclerosis in Austria. *Journal of Medical Economics* 2019;**22**(3):	Exclude RRMS Austria

Citation	Reason for exclusion
Walter E, Deisenhammer F. Socio-economic aspects of the testing for antibodies in MS-patients under interferon therapy in Austria: a cost of illness study. *Multiple Sclerosis and Related Disorders* 2014;**3**(6):	Exclude MS Austria
Wan GJ, Chopra I, Niewoehner J, Hunter SF. Cost per response analysis of repository corticotropin injection versus other alternative treatments for acute exacerbations of multiple sclerosis. *Drugs in Context* 2020;**9**	Exclude MS US
Watson C, Prosser C, Braun S, Landsman-Blumberg PB, Gleissner E, Naoshy S. Health care resource utilization before and after natalizumab initiation among patients with multiple sclerosis in Germany. *Clinicoeconomics & Outcomes Research* 2017;**9**	Exclude RRMS Germany
Watson C, Prosser C, Braun S, Landsman-Blumberg PB, Gleissner E, Naoshy S. Health care resource utilization before and after natalizumab initiation among patients with multiple sclerosis in Germany. *Clinicoeconomics & Outcomes Research* 2017;**9**	Exclude not an economic evaluation
Wilkinson SN, Dougall C, Kinsey-Henderson AE, Searle RD, Ellis RJ, Bartley R. Development of a time-stepping sediment budget model for assessing land use impacts in large river basins. *Science of the Total Environment* 2014;**468**	Exclude not an economic evaluation
Wilson S, Calocer F, Rollot F, Fauvernier M, Remontet L, Tron L*, et al.* Effects of socioeconomic status on excess mortality in patients with multiple sclerosis in France: A retrospective observational cohort study. *The Lancet Regional Health Europe* 2023;**24**	Exclude RRMS France
Wiyani A, Badgujar L, Khurana V, Adlard N. How have Economic Evaluations in Relapsing Multiple Sclerosis Evolved Over Time? A Systematic Literature Review. *Neurology and Therapy* 2021;**10**(2): 557-583	Exclude not an economic evaluation
Wiyani A, Badgujar L, Khurana V, Adlard N. How have Economic Evaluations in Relapsing Multiple Sclerosis Evolved Over Time? A Systematic Literature Review. *Neurology & Therapy* 2021;**10**(2):	Exclude not an economic evaluation
Xu Y, Mao N, Chirikov V, Du F, Yeh YC, Liu L*, et al.* Cost-effectiveness of Teriflunomide Compared to Interferon Beta-1b for Relapsing Multiple Sclerosis Patients in China. *Clinical Drug Investigation* 2019;**39**(3):	Exclude RRMS China
Yadlowsky S, Pellegrini F, Lionetto F, Braune S, Tian L. Estimation and Validation of Ratio-Based Conditional Average Treatment Effects Using Observational Data. *Journal of the American Statistical Association* 2021;**116**(533):	Exclude not an economic evaluation
Yang H, Duchesneau E, Foster R, Guerin A, Ma E, Thomas NP. Cost-effectiveness analysis of ocrelizumab versus subcutaneous interferon beta-1a for the treatment of relapsing multiple sclerosis. *Journal of Medical Economics* 2017;**20**(10):	Exclude RMS US
Zarco LA, Millan SP, Londono D, Parada L, Taborda A, Borda MG. [The cost-effectiveness of interferon beta treatment in patients with a clinically isolated syndrome in Colombia]. *Biomedica* 2014;**34**(1):	Exclude MS Colombia
Zarghami A, Fuh-Ngwa V, Claflin SB, Simpson-Yap S, Lucas R, Dear K*, et al.* Changes in employment status over time in multiple sclerosis following a first episode of central nervous system demyelination, a Markov multistate model study. *European Journal of Neurology* 2024;**31**	Exclude wrong population
Zhang X, Hay JW, Niu X. Cost effectiveness of fingolimod, teriflunomide, dimethyl fumarate and intramuscular interferon-beta1a in relapsing-remitting multiple sclerosis. *CNS Drugs* 2015;**29**(1):	Exclude RRMS China
Ziemssen T, Kurzeja A, Muresan B, Haas JS, Alexander J, Driessen MT. Real-world patient characteristics, treatment patterns and costs in relapsing multiple sclerosis patients treated with glatiramer acetate, dimethyl fumarate or teriflunomide in Germany. *Neurodegenerative Disease Management* 2022;**12**(2):	Exclude RRMS Germany
Zimmermann M, Brouwer E, Tice JA, Seidner M, Loos AM, Liu S*, et al.* Disease-Modifying Therapies for Relapsing-Remitting and Primary Progressive Multiple Sclerosis: A Cost-Utility Analysis. *CNS Drugs* 2018;**32**(12):	Exclude RRMS Germany

Appendix 3
Included study details

Study characteristics

Table 43 Overview of studies included in the review

Study Name	Population	Number enrolled	Duration (median follow-up)	Study Phase	Funding Sources	Study Location	MS Criteria	Previous treatment	Interventions evaluated
ADVANCE[80]	RRMS	1512	48 weeks (NR)	Phase III	Industry	183 sites in 26 countries	McDonald	Yes	Peginterferon beta 1a SC125
									Placebo
AFFIRM[77]	RRMS	943	2 years (NR)	Phase III	Industry	99 sites in Europe, North America, and New Zealand	McDonald	Yes	Natalizumab IV300
									Placebo
ANTELOPE[76]	RRMS	265	48 weeks (NR)	Phase III	Industry	48 sites in 7 countries	McDonald	Yes	Natalizumab IV300
									Natalizumab biosimilar
APOLITOS[69]	RRMS	64	24 weeks (NR)	Phase II	Industry	Japan and Russia	McDonald	Yes	Ofatumumab SC20
									Placebo
ASCLEPIOS I[68]	RRMS (94%)	927	30 months (1.5 years)	Phase III	Industry	385 sites in 37 countries	McDonald	Yes	Ofatumumab SC20
									Teriflunomide O14
ASCLEPIOS II[68]	RRMS (94%)	955	30 months (1.6 years)	Phase III	Industry		McDonald	Yes	Ofatumumab SC20
									Teriflunomide O14
ASSESS[81]	RRMS	1064	12 months (NR)	Phase III	Industry	127 sites in 6 countries	McDonald	Yes	Fingolimod O0.5
									Glatiramer acetate SC20
BEYOND[82]	RRMS	1345	2 years (NR)	Phase III	Industry	98 centres in 26 countries worldwide	McDonald	No	Interferon beta 1b SC250
									Glatiramer acetate SC20
Calabrese 2012[83]	RRMS	165	2 years (NR)	Phase IV	Industry	Italy	McDonald	No	Interferon beta 1a SC44
									Interferon beta 1a IM30
									Glatiramer acetate SC20
CAMMS223[84]	RRMS	334	36 months (NR)	Phase II	Industry	49 sites in Europe and the United States.	McDonald	No	Interferon beta 1a SC44
									Alemtuzumab IV12

Study Name	Population	Number enrolled	Duration (median follow-up)	Study Phase	Funding Sources	Study Location	MS Criteria	Previous treatment	Interventions evaluated
CARE-MS I[85]	RRMS	581	2 years (NR)	Phase III	Industry	101 sites in 16 countries	McDonald	No	Alemtuzumab IV12
									Interferon beta 1a SC44
CARE-MS II[71]	HARRMS	840	2 years (NR)	Phase III	Industry	194 sites in 23 countries	McDonald	Yes	Interferon beta 1a SC44
									Alemtuzumab IV12
CLARITY[86]	RRMS + HARRMS	1326	96 weeks (NR)	Phase III	Industry	155 sites in 32 countries	McDonald	Yes	Cladribine O3.5
									Placebo
CombiRx[87]	RRMS	1008	36 months (NR)	Phase III	Mixed	68 sites in USA and Canada	Poser or McDonald	Yes	Glatiramer acetate SC20
									Interferon beta 1a IM30
CONFIDENCE[88]	RRMS	861	6 months (NR)	Phase IV	Industry	14 countries	McDonald	Yes	Glatiramer acetate SC40
									Glatiramer acetate SC20
CONFIRM[89]	RRMS + HARRMS	1430	2 years (NR)	Phase III	Industry	200 sites in 28 countries	McDonald	Yes	Glatiramer acetate SC20
									Placebo
Copolymer 1 Multiple Sclerosis Study Group[90]	RRMS	251	2 years (NR)	Phase III	Mixed	USA	Poser	No	Glatiramer acetate SC20
									Placebo
Etemedifar 2006[91]	RRMS	90	2 years (NR)	NR	Not reported	Iran	Poser	No	Interferon beta 1b SC250
									Interferon beta 1a IM30
									Interferon beta 1a SC44
European/Canadian glatiramer acetate study group[92]	RRMS	239	9 months (NR)	NR	Industry	29 sites in 6 European countries and Canada	Poser	No	Glatiramer acetate SC20
									Placebo
EVIDENCE[93]	RRMS	677	48 weeks (NR)	NR	Industry	56 sites (15 in Europe, 5 in Canada, and 36in the United States)	Poser	No	Interferon beta 1a SC44
									Interferon beta 1a IM30
FREEDOMS[74]	RRMS + HARRMS	1272	2 years (NR)	Phase III	Industry	138 sites in 22 countries.	McDonald	Yes	Fingolimod O0.5
									Placebo
FREEDOMS II[73]	RRMS + HARRMS	1083		Phase III	Industry	117 sites in eight countries	McDonald	Yes	Fingolimod O0.5

Study Name	Population	Number enrolled	Duration (median follow-up)	Study Phase	Funding Sources	Study Location	MS Criteria	Previous treatment	Interventions evaluated
			24 months (NR)						Placebo
GALA[94]	RRMS	1404	1 year (NR)	Phase III	Industry	142 sites in 17 countries	McDonald	Yes	Glatiramer acetate SC40
									Placebo
GATE[95]	RRMS	796	9 months (NR)	Phase III	Industry	18 sites in 17 countries	McDonald	Yes	Glatiramer acetate SC20
									Placebo
GOLDEN[96]	RRMS	157	18 months (NR)	NR	Industry	36 sites 28 in Italy and 8 in Germany	McDonald	Yes	Fingolimod O0.5
									Interferon beta 1b SC250
IMPROVE[98]	RRMS	180	16 weeks double-blind then 24 week rater-blind (NR)	Phase III	Industry	International	McDonald	No	Interferon beta 1a SC44
									Placebo
INCOMIN[99]	RRMS	188	2 years (NR)	NR	Non-industry	15 sites in Italy	Poser	No	Interferon beta 1a IM30
									Interferon beta 1b SC250
IFNB Multiple Sclerosis Study Group[97]	RRMS	372	Unclear (NR)	NR	Industry	United States and Canada	Poser	No	Interferon beta 1b SC250
									Placebo
Kappos 2011[100]	RRMS	220	48 weeks (NR)	Phase II	Industry	International	McDonald	Yes	Ocrelizumab IV600
									Interferon beta 1a IM30
									Placebo
MIST[72]	HARRMS	110	Enrolment between 2005-2016, with final follow-up	NR	Non-industry	International	McDonald	Yes	AHSCT
									iDMT

Study Name	Population	Number enrolled	Duration (median follow-up)	Study Phase	Funding Sources	Study Location	MS Criteria	Previous treatment	Interventions evaluated
			in 2018 (2 years)						
Multiple Sclerosis Collaborative Research Group[105]	RRMS	301	2 years (NR)	Phase III	Mixed	USA	Poser	Yes	Interferon beta 1a IM30 Placebo
OPERA I[67]	RRMS + HARRMS	821	96 weeks (NR)	Phase III	Industry	141 trial sites across 32 countries	McDonald	Yes	Ocrelizumab IV600 Interferon beta 1a SC44
OPERA II[67]	RRMS + HARRMS	835	96 weeks (NR)	Phase III	Industry	166 trial sites across 24 countries	McDonald	Yes	Ocrelizumab IV600 Interferon beta 1a SC44
OPTIMUM[70]	RRMS (97%)	1133	108 weeks (NR)	Phase III	Industry	162 sites across 28 countries	McDonald	Yes	Ponesimod O20 Teriflunomide O14
PEGINTEGRITY[65]	RRMS	168	96 weeks (NR)	Phase III	Industry	9 sites in Iran	McDonald	No	Peginterferon beta 1a SC125 Interferon beta 1a IM30
Ponesimod Phase II study Group[101]	RRMS	387	24 weeks (NR)	Phase II	Industry	94 sites in 23 countries	McDonald	Yes	Ponesimod O20 Placebo
PRISMS[102]	RRMS	560	2 years (NR)	NR	Industry	22 sites in 9 countries	Poser	No	Interferon beta 1a SC22 Interferon beta 1a SC44 Placebo
REGARD[103]	RRMS	764	96 weeks (NR)	Phase IV	Industry	81 sites in 14 countries	McDonald	Yes	Interferon beta 1a SC44 Glatiramer acetate SC20
REVEAL[78]	RRMS	111	52 weeks (Natalizumab 40.1 weeks; Fingolimod 36.7 weeks)	Phase IV	Industry	43 sites in nine countries.	McDonald	Yes	Natalizumab IV300 Fingolimod O0.5

Study Name	Population	Number enrolled	Duration (median follow-up)	Study Phase	Funding Sources	Study Location	MS Criteria	Previous treatment	Interventions evaluated
Saida 2012[104]	RRMS (98%)	171	6 months (NR)	Phase II	Industry	43 centres in Japan	McDonald	No	Fingolimod O0.5
									Placebo
Saida 2017[79]	RRMS and close to HARRMS	94	24 weeks (NR)	Phase II	Industry	25 sites in Japan	McDonald	Yes	Natalizumab IV300
									Placebo
TRANSFORMS[75]	RRMS + HARRMS	1291	12 months (NR)	Phase III	Industry	172 sites in 18 countries.	McDonald	Yes	Fingolimod O0.5
									Interferon beta 1a IM30

Included studies and reports

Table 44 Studies included in the review showing primary and related reports and whether additional data were extracted from related reports

Study Name	Report	Additional Data report
ADVANCE	Primary report[80]	NA
	Related report - data extracted[198]	Quality of life data
	Related report - no relevant data[199]	no evidence of disease - NEDA data
	Related report - no relevant data[200]	Post hoc analysis of evolution of MRI lesions
	Related report - no relevant data[201]	Pharmacokinetics and pharmacodynamics data
	TA624[32]	Additional data on disease progression
AFFIRM	Primary report[77]	NA
	Related report - data extracted[202]	Reports on AFFIRM and SENTINEL EDSS
	Related report - no relevant data[203]	Visual outcomes
	Related report - no relevant data[204]	Free from disease activity
	Related report - no relevant data[205]	Data in patients who have relapsed
	Related report - no relevant data[206]	MRI outcomes
	Related report - no relevant data[207]	MRI outcomes
	Trial Registry Entry[208]	NA
AFFIRM/SENTINEL	Synthesis across related studies[209]	Visual outcomes
	Synthesis across related studies[210]	Participants of African descent
	Synthesis across related studies[211]	Subgroup analyses
	TA127[34]	Additional data on disease progression; additional potentially relevant data on disease progression redacted
AFFIRM/TIMER	Synthesis across related studies[212]	Ambulation outcomes
ANTELOPE	Primary report[76]	NA
	Trial Registry Entry[213]	NA
APOLITOS	Primary report[69]	NA
ASCLEPIOS I/II	Primary report[68]	NA
	Related report - no relevant data[214]	Sub analysis on treatment naïve patients

Study Name	Report	Additional Data report
	Trial registry[215]	NA
	TA699[41]	No additional data – data for highly active population redacted
ASSESS	Primary report[81]	NA
	Trial Registry Entry[216]	NA
BEYOND	Primary report[82]	NA
	Related report - no relevant data[217]	Additional MRI outcomes (black hole development)
Calabrese 2012	Primary report[83]	NA
CAMMS223	Primary report[84]	NA
	Related report - no relevant data[218]	Subgroup analyses, freedom from disease activity, sustained disability reduction
	Related report - no relevant data[219]	Follow-up of 6 patients with thrombocytopenia
	Related report - no relevant data[220]	Thyroid dysfunction outcome data
	Related report - no relevant data[221]	individual functional scores of EDSS outcomes
	Related report - no relevant data[222]	Visual outcomes
	Trial Registry Entry[223]	NA
	TA312[39]	No additional data; data on QoL redacted
CARE-MS I	Primary report[85]	NA
	Trial Registry Entry[224]	NA
	Trial Registry Entry[225]	NA
	TA312[39]	No additional data
CARE-MS II	Primary report[71]	NA
	Related report - no relevant data[226]	QoL Data
	Related report - no relevant data[227]	Additional EDSS data
	Trial Registry Entry[228]	NA
	Trial Registry Entry[229]	NA
	Trial Registry Entry[230]	NA
	TA312[39]	No additional data
CARE-MS I/II	Synthesis across related studies[231]	Additional MRI outcomes
	Synthesis across related studies[232]	QoL data
	Synthesis across related studies[233]	Neutropenia

Study Name	Report	Additional Data report
	Synthesis across related studies[234]	Post-hoc analysis looking at age
	Synthesis across related studies[235]	QoL - FAMS only
	Synthesis across related studies[236]	Safety data in Russian patients
CLARITY	Primary report[86]	NA
	Related report - data extracted[237]	QoL data
	Related report - data extracted[238]	Additional data on freedom from disease activity
	Related report - highly active population[239]	Data extracted for this population
	Related report - no relevant data[240]	Additional MRI outcomes
	Related report - no relevant data[241]	Additional safety data
	Related report - no relevant data[242]	Additional MRI outcomes
	Related report - no relevant data[243]	Brain volume changes
	Related report - no relevant data[244]	Relapses in main and extension trial
	Related report - no relevant data[245]	Additional data on highly active subgroup
	Related report - no relevant data[246]	Cardiac outcomes
	Related report - no relevant data[247]	Subgroup data including rapidly evolving severe MS
	Trial Registry Entry[248]	NA
	Trial Registry Entry[249]	NA
	TA616[38]	No additional data
CLARITY/CARE-MS-I	Synthesis across related studies[250]	lymphocyte data
CombiRx	Primary report[87]	NA
	Related report - no relevant data[251]	Risk factors for early treatment failure
	Related report - no relevant data[252]	Designs and baseline characteristics
	Related report - no relevant data[253]	Imaging biomarker data
CONFIDENCE	Primary report[88]	NA
CONFIRM	Primary report[89]	NA
	Related report - data extracted[254]	quality of life data
	Related report - highly active population[255]	subgroup analyses

Study Name	Report	Additional Data report
	Related report - no relevant data[256]	Effect of DF on MRI measures
	Synthesis across related studies[257]	Effect of DF on prior interferon users
	Synthesis across related studies[258]	Effect of DF on no evidence of disease
	Trial Registry Entry[259]	NA
Copolymer 1 Multiple Sclerosis Study Group	Primary report[90]	NA
	Related report - no relevant data[260]	Area under disability time curves
	Related report - no relevant data[261]	Neuropsychological outcomes
	Trial Registry Entry[262]	NA
Etemedifar 2006	Primary report[91]	NA
European/Canadian glatiramer acetate study group	Primary report[92]	NA
	Related report - no relevant data[263]	Additional MRI Outcomes
EVIDENCE	Primary report[93]	
	Related report - data extracted[264]	outcomes at 16 months
	Related report - data extracted[265]	Data for comparative phase and crossover phase
	Related report - no relevant data[266]	data on NEDA
	Related report - no relevant data[267]	specific safety and tolerability data
	Related report - no relevant data[268]	data after crossover
	Related report - no relevant data[269]	MRI T2 burden of disease data
FREEDOMS	Primary report[74]	NA
	Related report - data extracted[270]	Highly active subgroup data
	Related report - no relevant data[271]	Post hoc analysis of subgroups based on previous treatments
	Related report - no relevant data[272]	Additional MRI data
	Trial Registry Entry[273]	NA
	Trial Registry Entry[274]	NA
	TA254[40]	Baseline data for HA population; redacted data on: baseline relapse rate, HR for disability progression in highly active population and EQ-5D data
FREEDOMS II	Primary report[73]	NA
	Related report - no relevant data[275]	Corrections to paper
	Trial Registry Entry[276]	NA

Study Name	Report	Additional Data report
	Trial Registry Entry[277]	NA
FREEDOMS/ FREEDOMS II	Synthesis across related studies[278]	MRI brain volume
	Synthesis across related studies[108]	Highly active subgroup
	Synthesis across related studies[279]	MRI outcomes
	Synthesis across related studies[280]	Early (3 and 6 months) outcomes
FREEDOMS/ FREEDOMS II/ TRANSFORMS	Synthesis across related studies[281]	Hispanic patients
	Synthesis across related studies[282]	Relapse rates in different patient subgroups
FREEDOMS/ TRANSFORMS	Synthesis across related studies[283]	Hungarian poster with clinical and MRI outcomes
GALA	Primary report[94]	NA
	Related report - data extracted[284]	post-hoc analysis of the study but think it is just focusing on a russian patient subset?
	Related report - no relevant data[285]	Timing of efficacy onset
	Related report - no relevant data[286]	looks at total t1 lesions vs t1 non enhanced lesions
	Trial Registry Entry[287]	NA
GATE	Primary report[95]	NA
	Trial Registry Entry[288]	NA
GOLDEN	Primary report[96]	NA
	Trial Registry Entry[289]	NA
	Trial Registry Entry[290]	NA
IFNB Multiple Sclerosis Study Group	Primary report[97]	NA
	Related report - data extracted[291]	Additional MRI data
	Related report - data extracted[292]	Additional MRI data
	Related report - no relevant data[293]	Additional MRI data
	Related report - no relevant data[294]	Additional MRI data
IMPROVE	Primary report[98]	NA
	Related report - data extracted[295]	baseline data
	Related report - no relevant data[296]	Other MRI outcomes
	Trial Registry Entry[297]	NA
	Trial Registry Entry[298]	NA

Study Name	Report	Additional Data report
INCOMIN	Primary report[99]	NA
	Related report - no relevant data[299]	Additional MRI outcomes
Kappos2011	Primary report[100]	NA
	Trial Registry Entry[300]	NA
	Trial Registry Entry[301]	NA
MIST	Primary report[72]	NA
	Trial Registry Entry[302]	NA
Multiple Sclerosis Collaborative Research Group	Primary report[105]	NA
	Related report - no relevant data[303]	Baseline details
	Related report - no relevant data[304]	Additional data on disability
OPERA I/II	Primary report[67]	NA
	Synthesis across related studies[305]	Brain volume
	Synthesis across related studies[306]	MRI outcomes
	Synthesis across related studies[307]	Data for participants of African descent
	Synthesis across related studies[308]	Risk of requiring walking aid after 6.5 years - open label extension
	Synthesis across related studies[309]	Infusion related reactions
	Synthesis across related studies[310]	Data for highly active disease
	Synthesis across related studies[311]	Subgroup of patients with increased disability at baseline
	NICE TA533[33]	Additional data on highly active disease (combined across both trials); redacted data on EQ-5D
OPTIMUM	Primary report[70]	NA
	Related report - no relevant data [312]	Subgroup analysis in women
	Trial registry entry[313]	NA
	TA767[42]	No additional data – data for highly active population redacted
PEGINTEGRITY	Primary report[65]	NA
	Trial Registry Entry[314]	NA
Ponesimod Phase II study Group	Primary report[101]	NA
	Related report - no relevant data[315]	Erratum relating to Figure
	Synthesis across related studies[316]	Core and extension studies
	Trial Registry Entry[317]	NA

Study Name	Report	Additional Data report
PRISMS	Primary report[102]	NA
	Related report - data extracted[318]	MRI outcomes
	Related report - data extracted[319]	NEDA data
	Related report - no relevant data[320]	Erratum relating to author COI
	Related report - no relevant data[321]	Additional EDSS outcomes
	Related report - no relevant data[322]	Additional EDSS outcomes
	Related report - no relevant data[323]	Depression outcomes
PRISMS/SPECTRIMS	Synthesis across related studies[324]	Posthoc analysis of combined data
	Synthesis across related studies[325]	MRI outcomes
REGARD	Primary report[103]	NA
	Trial Registry Entry[326]	NA
REVEAL	Primary report[78]	NA
	Trial Registry Entry[327]	NA
	Trial Registry Entry[328]	NA
Saida 2012	Primary report[104]	NA
Saida 2017	Primary report[79]	NA
	Trial Registry Entry[329]	NA
	Related report - no relevant data[330]	subanalysis of patients who achieved no evidence of disease
TRANSFORMS	Primary report[75]	NA
	Related report - no relevant data[331]	MRI brain volume outcomes
	Related report - no relevant data[332]	Highly active and other subgroup data but not in format for inclusion
	Related report - no relevant data[333]	subgroup analysis
	Trial Registry Entry[334]	NA
	Trial Registry Entry[335]	NA

Baseline characteristics

Table 45 Baseline participant details (RRMS population)

Study Name	Treatment arm	N	Age (sd)	% Female	Years from diagnosis (SD)	EDSS (SD)	% White	% Black	% Asian	% Other	Annual Relapse rate (SD)	% treated	Previous treatments
ADVANCE[80]	Placebo	500	36.3 (9.7)	72	3.5(4.6)	2.4 (1.2)	82	0.6	11	6	1.6(0.7)	7	DMT
	Peginterferon beta 1a SC125	512	36.9 (9.8)	71	4(5.1)	2.5 (1.3)	81	0.58	12	7	1.6(0.7)	8	
AFFIRM[77]	Natalizumab IV300	627	35.6 (8.5)	72	NR(NR)	2.3 (1.2)	96	NR	NR	4	1.5(0.9)	9	interferon beta-1a interferon beta-1b or glatiramer acetate
	Placebo	315	36.7 (7.8)	67	NR(NR)	2.3 (1.2)	94	NR	NR	6	1.5(0.8)	8	
ANTELOPE[76]	Natalizumab biosimilar	131	36.8 (9.1)	64.1	5.3(4.7)	3.4 (1.1)	100	0	0	0	1.4(0.7)	NR	NR
	Natalizumab IV300	133	36.6 (9.7)	58.6	5.3(4.8)	3.2 (1.2)	100	0	0	0	1.4(0.6)	NR	
APOLITOS[69]	Ofatumumab SC20	43	35 (9.5)	83.7	5.1(6.3)	2.2 (1)	51.2	NR	48.8	NR	1.6(0.9)	67	interferon beta; glatiramer; dimethyl fumarate; fingolimod; natalizumab; other DMTS
	Placebo	21	35.5 (8.9)	90.5	6(6.4)	2.2 (1.3)	47.6	NR	52.4	NR	1.2(0.7)	71	
ASCLEPIOS I[68]	Ofatumumab SC20	465	38.9 (8.8)	68	5.8 (6.1)	3.0 (1.4)	88	3	3	5	1.2(0.6)	59	interferon beta, glatiramer acetate, dimethyl fumarate,
	Teriflunomide O14	462	37.8 (9.0)	69	5.6 (6.2)	3.0 (1.4)	89	4	4	3	1.3(0.7)	61	
ASCLEPIOS II[68]	Ofatumumab SC20	481	38.0 (9.3)	66	5.6 (6.4)	2.9 (1.3)	87	3	4	4	1.3(0.7)	60	

Study Name	Treatment arm	N	Age (sd)	% Female	Years from diagnosis (SD)	EDSS (SD)	% White	% Black	% Asian	% Other	Annual Relapse rate (SD)	% treated	Previous treatments
	Teriflunomide O14	474	38.2 (9.5)	67	5.5 (6.0)	2.9 (1.4)	88	4	4	3	1.3(0.7)	62	natalizumab, B-cell therapy, lanquinimod, other DMT
ASSESS[81]	Fingolimod O0.5	352	40.3 (11.1)	75	4.3(5.9)	2.7 (1.5)	76.1	9.7	0	11.9	1.4(0.8)	52	NR
	Glatiramer acetate SC20	342	39.6 (10.8)	73.7	4.7(6.2)	2.7 (1.4)	71.1	12	0	14.3	1.4(0.8)	55	
BEYOND[82]	Interferon beta 1b SC250	897	35.8 (IQR 28-43)	70	5.3(NR)	2.4 (IQR 1.5-3.0)	93	NR	NR	NR	1.6(NR)	0	None
	Glatiramer acetate SC20	448	35.2 (IQR 27-43)	68	5.1(NR)	2.3 (IQR 1.5-3.1)	91	NR	NR	NR	1.6(NR)	0	
Calabrese 2012[83]	Interferon beta 1a SC44	46	35.9 (9.1)	69.5	5.7(4.9)	1.9 (1)	NR	NR	NR	NR	1.2(0.6)	NR	NR
	Interferon beta 1a IM30	47	34.8 (9.6)	68	5.3(5.1)	1.9 (0.8)	NR	NR	NR	NR	1.2(0.7)	NR	
	Glatiramer acetate SC20	48	38.9 (10.2)	72.9	5.5(6.1)	2.1 (1.1)	NR	NR	NR	NR	1.3(0.7)	NR	
CAMMS223[84]	Interferon beta 1a SC44	111	32.8 (8.8)	64	NR(NR)	1.9 (0.8)	90.1	NR	NR	NR	NR	0	None
	Alemtuzumab IV12	112	31.9 (8.0)	64.3	NR(NR)	1.9 (0.7)	91.1	NR	NR	NR	NR	0	
CARE-MS I[85]	Interferon beta 1a SC44	187	33.2 (8.5)	65	2(1.3)	2 (0.8)	96	NR	NR	NR	1.8(0.8)	0	None
	Alemtuzumab IV12	376	33 (8.0)	65	2.1(1.4)	2 (0.8)	94	NR	NR	NR	1.8(0.8)	0	
CLARITY[86]	Placebo	437	38.7 (9.9)	65.9	8.9(7.4)	2.9 (1.3)	98.2	0.2	NR	1.6	NR	33	interferon beta 1a, interferon beta 1b, glatiramer acetate
	Cladribine O3.5	433	37.9 (10.3)	68.8	7.9(7.2)	2.8 (1.2)	98.2	0.5	NR	1.4	NR	32	

Study Name	Treatment arm	N	Age (sd)	% Female	Years from diagnosis (SD)	EDSS (SD)	% White	% Black	% Asian	% Other	Annual Relapse rate (SD)	% treated	Previous treatments
CombiRx[87]	Glatiramer acetate SC20	259	39 (9.5)	71.4	1(2.9)	1.9 (1.2)	90.3	NR	NR	NR	1.6(0.7)	NR	NR
	Interferon beta 1a IM30	250	37.6 (10.2)	69.2	1.4(4)	2 (1.2)	84.8	NR	NR	NR	1.7(0.9)	NR	
CONFIDENCE[88]	Glatiramer acetate SC40	431	41 (11.2)	66.8	5.7(6.5)	2.2 (1.3)	83.3			16.7	0.8(0.9)	60	Any DMT
	Glatiramer acetate SC20	430	40.1 (10.7)	71.4	5.6(6.3)	2.1 (1.3)	84.4			15.6	0.7(0.7)	59	
CONFIRM[89]	Placebo	363	36.9 (9.2)	69	4.8(5)	2.6 (1.2)	84	2	8	6	1.4(0.8)	31	interferon beta 1a, interferon beta 1b, glatiramer, natalizumab
	Glatiramer acetate SC20	350	36.7 (9.1)	71	4.4(4.7)	2.6 (1.2)	83	3	7	7	1.4(0.6)	29	
Copolymer 1 Multiple Sclerosis Study Group[90]	Glatiramer acetate SC20	125	34.6 (6)	70.4	7.3(4.9)	2.8 (1.2)	94.4	NR	NR	5.6	1.5(0.7)	NR	NR
	Placebo	126	34.3 (6.5)	76.2	6.6(5.1)	2.4 (1.3)	93.6	NR	NR	6.3	1.5(0.6)	NR	
Etemedifar 2006[91]	Interferon beta 1b SC250	30	NR (NR)	30.9	3.7(2.3)	NR (NR)	NR	NR	NR	NR	2.2(0.7)	NR	NR
	Interferon beta 1a IM30	30	NR (NR)	35.3	2.9(2.3)	NR (NR)	NR	NR	NR	NR	2.0(0.8)	NR	
	Interferon beta 1a SC44	30	NR (NR)	33.8	3.0(2.2)	NR (NR)	NR	NR	NR	NR	2.4(1.0)	NR	
European/ Canadian glatiramer acetate study group[92]	Glatiramer acetate SC20	119	34.1 (7.4)	NR	7.9(5.5)	2.3 (1.1)	NR	NR	NR	NR	1.4(0.9)	NR	NR
	Placebo	120	34 (7.5)	NR	8.3(5.5)	2.4 (1.2)	NR	NR	NR	NR	1.2(0.7)	NR	
EVIDENCE[93]	Interferon beta 1a SC44	339	38.3 (NR)	74.9	4.0(6.5)	2.0 (2.3)	92.3	NR	NR	NR	2.0(2.6)	0	None

Study Name	Treatment arm	N	Age (sd)	% Female	Years from diagnosis (SD)	EDSS (SD)	% White	% Black	% Asian	% Other	Annual Relapse rate (SD)	% treated	Previous treatments
	Interferon beta 1a IM30	338	37.4 (NR)	74.6	4.1(6.7)	2.0 (2.3)	89.6	NR	NR	NR	2.0(2.6)	0	
FREEDOMS[74]	Fingolimod O0.5	425	36.6 (8.8)	69.6	8.0(6.6)	2.3 (1.3)	NR	NR	NR	NR	1.5(0.8)	43	Interferon beta 1a, interferon beta 1b, glatiramer acetate,
	Placebo	418	37.2 (8.6)	71.3	8.1(6.4)	2.5 (1.3)	NR	NR	NR	NR	1.4(0.7)	40	
FREEDOMS II[73]	Fingolimod O0.5	358	40.6 (8.4)	77	10.4(8.0)	2.4 (1.3)	NR	NR	NR	NR	1.4(0.9)	74	Interferon beta 1a, interferon beta 1b, glatiramer acetate, natalizumab
	Placebo	355	40.1 (8.4)	81	10.6(7.9)	2.4 (1.3)	NR	NR	NR	NR	1.5(0.9)	73	
GALA[94]	Glatiramer acetate SC40	943	37.4 (9.4)	68	NR	2.8 (1.2)	97.1	1.3	0.2	1.4	1.3(0.6)	14	Prior DMT treatment
	Placebo	461	38.1 (9.2)	67.9	NR(NR)	2.7 (1.2)	98.7	0.7	0	0.6	1.3(0.6)	14	
GATE[95]	Glatiramer acetate SC20	357	33.8 (9)	66.7	6.4(6)	2.7 (1.2)	NR	NR	NR	NR	0.9(0.5)	83	NR
	Placebo	84	32.6 (8.7)	67.9	5.7(6)	2.7 (1.2)	NR	NR	NR	NR	0.9(0.5)	88	
GOLDEN[96]	Fingolimod O0.5	104	39.5 (9.3)	65.4	NR(NR)	NR (NR)	NR	NR	NR	NR	NR	NR	NR
	Interferon beta 1b SC250	47	37.5 (9.3)	63.8	NR(NR)	NR (NR)	NR	NR	NR	NR	NR	NR	
IFNB Multiple Sclerosis Study Group[336]	Placebo	123	36.0 (6.7)	NR	3.9(3.3)	2.8 (1.1)	94.3	NR	NR	5.7	1.8(0.6)	0	No
	Interferon beta 1b SC250	124	35.2 (6.7)	NR	4.7(4.5)	3.0 (1.1)	93.6	NR	NR	6.4	1.7(1.1)	0	No
IMPROVE[98]	Placebo	60	35.2 (10.5)	70	NR(NR)	2.3 (NR)	NR	NR	NR	NR	NR	NR	NR
	Interferon beta 1a SC44	120	34 (7.8)	73.3	NR(NR)	2.5 (NR)	NR	NR	NR	NR	NR	NR	

Study Name	Treatment arm	N	Age (sd)	% Female	Years from diagnosis (SD)	EDSS (SD)	% White	% Black	% Asian	% Other	Annual Relapse rate (SD)	% treated	Previous treatments
INCOMIN[99]	Interferon beta 1a IM30	92	34.9 (7.9)	62	6.7(5.4)	2 (0.7)	NR	NR	NR	NR	1.4(0.5)	0	None
	Interferon beta 1b SC250	96	38.8 (7.1)	69	5.9(4.2)	2 (0.7)	NR	NR	NR	NR	1.5(0.7)	0	
Kappos 2011[100]	Placebo	54	38 (8.8)	67	2.7(0.1-19.2)	3.2 (1.4)	96	NR	NR	NR	NR	30	β interferons, glatiramer acetate, intravenous immuno-globulin, plasmaphere sis, and immune-suppresive treatment
	Ocrelizumab IV600	55	35.6 (8.5)	64	3.6(0.1-16.5)	3.5 (1.5)	93	NR	NR	NR	NR	53	
	Interferon beta 1a IM30	54	38.1 (9.3)	59	3.3(0.1-20.2)	3.1 (1.5)	98	NR	NR	NR	NR	31	
Multiple Sclerosis Collaborative Research Group[105]	Interferon beta 1a IM30	158	36.7 (8.0)	75	6.6(6.2)	2.4 (0.9)	93	7	NR	0	1.2(0.6)	NR	NR
	Placebo	143	36.9 (6.8)	72	6.4(5.5)	2.3 (0.7)	92	6	NR	2	1.2(0.6)	NR	NR
OPERA I[67]	Ocrelizumab IV600	410	37.1 (9.3)	65.9	3.8(4.8)	2.9 (1.2)	NR	NR	NR	NR	1.3(0.7)	26	Interferon, Glatiramer acetate, Fingolimod, Dimethyl fumarate, Other (NR)
	Interferon beta 1a SC44	411	36.9 (9.3)	66.2	3.7(4.6)	2.8 (1.3)	NR	NR	NR	NR	1.3(0.6)	29	Interferon, Glatiramer acetate, Natalizumab, Other (NR)

Study Name	Treatment arm	N	Age (sd)	% Female	Years from diagnosis (SD)	EDSS (SD)	% White	% Black	% Asian	% Other	Annual Relapse rate (SD)	% treated	Previous treatments
OPERA II[67]	Ocrelizumab IV600	417	37.2 (9.1)	65	4.2(5)	2.8 (1.3)	NR	NR	NR	NR	1.3(0.7)	27	Interferon, Glatiramer acetate, Natalizumab, Fingolimod, Other (NR)
	Interferon beta 1a SC44	418	37.4 (9.0)	67	4.1(5.1)	2.8 (1.4)	NR	NR	NR	NR	1.3(0.7)	25	Interferon, Glatiramer acetate, Other (NR)
OPTIMUM[70]	Ofatumumab SC20	567	36.7 (8.7)	64	7.6 (6.8)	2.6 (1.2)	97	0.5	NR	2.3	1.2 (0.6)	38	Interferon beta 1a, interferon beta 1b, or glatiramer acetate
	Teriflunomide O14	566	36.8 (8.7)	66	7.7 (6.8)	2.6 (1.2)	98	0.4	NR	2.0	1.3 (0.7)	37	
PEGINTEGRITY[65]	Peginterferon beta 1a SC125	84	30 (6.5)	84.52	NR(NR)	1.1 (0.9)	NR	NR	NR	NR	NR	0	None
	Interferon beta 1a IM30	84	30.8 (7.4)	83.33	NR(NR)	1 (0.8)	NR	NR	NR	NR	NR	0	
Ponesimod Phase II study Group[101]	Ponesimod O20	116	35.5 (8.5)	67.5	NR(NR)	2.2 (1.3)	98.2	NR	NR	NR	NR	NR	NR
	Placebo	121	36.6 (8.6)	70.2	NR(NR)	2.2 (1.2)	94.2	NR	NR	NR	NR	NR	
PRISMS[102]	Placebo	187	34.6 (NR)	75	NR(NR)	2.4 (1.2)	NR	NR	NR	NR	1.5(0.7)	0	None
	Interferon beta 1a SC22	189	34.8 (NR)	67	NR(NR)	2.5 (1.2)	NR	NR	NR	NR	1.5(0.6)	0	
	Interferon beta 1a SC44	184	35.6 (NR)	66	NR(NR)	2.5 (1.3)	NR	NR	NR	NR	1.5(0.6)	0	
REGARD[103]	Interferon beta 1a SC44	386	36.7 (9.8)	69	NR(NR)	2.4 (1.3)	93%	4%	<1%	2%	NR	NR	NR
	Glatiramer acetate SC20	378	36.8 (9.5)	72	NR(NR)	2.3 (1.3)	94%	4%	<1%	2%	NR	NR	

Study Name	Treatment arm	N	Age (sd)	% Female	Years from diagnosis (SD)	EDSS (SD)	% White	% Black	% Asian	% Other	Annual Relapse rate (SD)	% treated	Previous treatments
REVEAL[78]	Natalizumab IV300	54	38.2 (8.8)	68.5	5(5.8)	NR (NR)	NR	NR	NR	NR	1.9(0.7)	48	Less than 6 months of glatiramer acetate or interferon beta
	Fingolimod O0.5	54	34.9 (8.7)	70.4	4.5(5.8)	NR (NR)	NR	NR	NR	NR	1.9(0.6)	52	
Saida 2012[104]	Placebo	57	35 (8.9)	68.4	8.2(7.3)	NR (NR)	0	0	100	0	1.7(1.6)	NR	NR
	Fingolimod O0.5	57	35 (9)	70.2	8.2(6.8)	NR (NR)	0	0	100	0	1.4(1.0)	NR	
Saida 2017[79]	Natalizumab IV300	47	37.7 (8.6)	72	5.9(5)	2.5 (1.6)	0	0	100	0	2.0(1.2)	91	IFN beta 1a, IFN beta 1b, azathioprine, fingolimod
	Placebo	47	35.1 (8.2)	68	5.1(4.9)	2.1 (1.5)	0	0	100	0	1.9(1.0)	85	
TRANSFORMS[75]	Fingolimod O0.5	431	36.7 (8.8)	65.4	7.5(6.2)	2.2 (1.3)	94.8	NR	NR	NR	1.5(1.2)	55	Interferon beta, glatiramer acetate, natalizumab
	Interferon beta 1a IM30	435	36 (8.3)	67.8	7.4(6.3)	2.2 (1.3)	93.8	NR	NR	NR	1.5(0.8)	56	

Table 46 Baseline participant details (HARRMS population)

Study Name	Treatment arm	N	Age (sd)	% Female	Years from diagnosis (SD)	EDSS (SD)	Annual Relapse rate (SD)	% treated	Previous treatments	Highly active definition
CLARITY[86]	Placebo	56	37.5 (9.3)	71.4	NR	NR	NR	100	Interferon beta 1a, interferon beta 1b, glatiramer acetate	≥ 2 relapses in previous year or ≥1 relapse and ≥1 T1 Gd+ or ≥9 T2 lesions
	Cladribine O3.5	46	36.6 (8.6)	71.7	NR	NR	NR	100		
CARE-MS II[71]	Interferon beta 1a SC44	202	35.8 (8.8)	65	4.7(2.9)	2.7 (1.2)	1.5(0.8)	100	interferon beta, glatiramer, natalizumab, immunoglobulin, azathioprine	≥ 2 relapses in previous 2 years with at ≥1 in previous year; at least one relapse while on interferon beta or glatiramer after at least 6 months of treatment
	Alemtuzumab IV12	426	34.8 (8.4)	66	4.5(2.7)	2.7 (1.3)	1.7(0.9)	100		
FREEDOMS I & II[73]	Fingolimod O0.5	249	39.3 (8.8)	76.3	6.3(5.6)	2.5 (1.3)	1.5(0.8)	100	Interferon beta 1a SC, interferon beta 1a IM, interferon beta 1b SC, glatiramer acetate, natalizumab	(1) ≥1 relapse in the previous year and either ≥1 gadolinium (Gd) enhancing T1 lesion or ≥9 T2 lesions at baseline and/or (2) as many or more relapses in the year before baseline as in the previous year
	Placebo	257	39.2 (8.4)	74.7	6.2(5.5)	2.7 (1.4)	1.6(0.9)	100		
MIST[72]	AHSCT	55	35.6 (8.4)	62	5.3 (3.7)	3.4 (1.2)	NR	100	glatiramer acetate, interferon beta 1a, interferon beta 1b, dimethyl fumarate, natalizumab, intravenous immunoglobulin, fingolimod, teriflunomide, azathioprine, methotrexate	2 or more clinical relapses or 1 relapse and MRI gadolinium-enhancing lesion(s) at a separate time within the previous 12 months despite receiving treatment with DMT
	iDMT	55	35.6 (8.2)	66	7.1 (5.1)	3.3 (1)	NR	100		
OPERA I & II combined[67]	Ocrelizumab IV600	143	NR	NR	NR	NR	NR	NR	NR	

Study Name	Treatment arm	N	Age (sd)	% Female	Years from diagnosis (SD)	EDSS (SD)	Annual Relapse rate (SD)	% treated	Previous treatments	Highly active definition
	Interferon beta 1a SC44	140	NR	NR	NR	NR	NR	NR		Treated with interferons or glatiramer acetate for at least 1 year, and • ≥1 relapse in previous year • ≥1 least one T1 Gd-enhancing lesion on brain MRI at baseline • ≥1 9 T2 hyperintense lesions on brain MRI at baseline
Saida 2017[79]	Natalizumab IV300	47	37.7 (8.6)	72	5.9(5)	2.5 (1.6)	2.0(1.2)	91	IFN beta 1a, IFN beta 1b, azathioprine, fingolimod	Not fully HARRMS; one relapse in previous year but only 88% received previous DMT
	Placebo	47	35.1 (8.2)	68	5.1(4.9)	2.1 (1.5)	1.9(1.0)	85		
TRANSFORMS[75]	Fingolimod O0.5	189	37.1 (8.8)	70.9	6.4(4.7)	2.5 (1.4)	NR	100	Beta interferon, glatiramer acetate, natilizumab	Patients who received DMT in the previous year with unchanged or increased relapse rate or ongoing severe relapses as compared with the previous year
	Interferon beta 1a IM30	191	37.1 (8.4)	67.5	6.8(6)	2.4 (1.2)	NR	100		

Appendix 4
Included study results and outcome definitions

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Table 47 Definitions of relapse, broken down into definition components, used in each of the included trials

Study Name	Symptoms	Symptom duration	Absence of	EDSS/neurological examination	Preceding stability period	Verification
ADVANCE[80]	New or recurrent neurologic symptoms	≥ 24 hours	Fever or infection	New objective neurologic findings	NR	Independent neurological evaluation committee
AFFIRM[77]	New or recurrent neurologic symptoms	≥ 24 hours	Fever or infection	New objective neurologic findings	NR	Examining neurologist
ANTELOPE[76]	New or worsening neurologic symptom	≥ 24 hours	Fever or infection	NR	≥30 days	NR
APOLITOS[69]	Symptoms (not defined)	NR	NR	EDSS increase ⩾0.5 points, or increase ⩾1 on two functional scores or ⩾2 on one	NR	NR
ASCLEPIOS I[68]	New or worsening neurologic symptom	≥ 24 hours	Fever or infection	EDSS increase ⩾0.5 points, or increase ⩾1 on two functional scores or ⩾2 on one	≥30 days	Investigator
ASSESS[81]	Symptoms (not defined)	NR	NR	EDSS increase ⩾0.5 points, or increase ⩾1 on two functional scores or ⩾2 on one	NR	Examiner ≤ 7 days of notification
BEYOND[82]	New or recurrent neurologic symptoms	≥ 24 hours	Fever or infection	Increase in EDSS or functional system scores	≥30 days	Evaluating physician
Calabrese 2012[83]	Definition not reported	NR	NR	NR	NR	NR
CAMMS223[84]	New or worsening symptoms	≥ 48 hours	Fever	New objective neurologic findings attributable to MS that	≥30 days	NR
CARE-MS I[85]	New or worsening neurologic symptom	≥ 48 hours	NR	New objective neurologic findings	≥30 days	Masked examiner

Study Name	Symptoms	Symptom duration	Absence of	EDSS/neurological examination	Preceding stability period	Verification
CARE-MS II[71]	New or worsening neurologic symptom attributable to MS	≥ 48 hours	Fever	Objective change on neurological examination.	≥30 days	NR
CLARITY[86]	Symptoms (not defined)	≥ 24 hours	Fever	EDSS increase ⩾0.5 points, or increase ⩾1 on two functional scores or ⩾2 on one	≥30 days	NR
CombiRx[87]	New or worsening neurologic symptom attributable to MS	≥ 24 hours	NR	EDSS increase ⩾0.5 points, or increase ⩾1 on two functional scores or ⩾2 on one	≥30 days	NR
CONFIDENCE[88]	*Did not report on relapse rate*					
CONFIRM[89]	New or recurrent neurologic symptoms	≥ 24hours	Fever or infection	New objective neurologic findings	≥30 days	NR
Copolymer 1 Multiple Sclerosis Study Group[90]	New or recurrent neurologic symptoms	≥ 48 hours	Fever	EDSS increase ⩾0.5 points, or an increase or ⩾2 on one functional score	≥30 days	NR
Etemedifar 2006[91]	New or severely worsening neurologic symptom	≥ 24 hours	NR	EDSS increase ⩾1 point	NR	NR
European/Canadian glatiramer acetate study group[92]	New or recurrent neurologic symptoms	≥ 48 hours	NR	EDSS increase ⩾0.5 points, or increase ⩾1 on two functional scores or ⩾2 on one	≥30 days	Visit ≤ 7 days of notification.
EVIDENCE[93]	New or worsening neurologic symptom	≥ 24 hours	Fever	Objective change on neurological examination.	≥30 days	NR
FREEDOMS[74]	Symptoms (not defined)	NR	NR	EDSS increase ⩾0.5 points, or increase ⩾1 on two functional scores or ⩾2 on one	NR	Examining neurologist ≤ 7 days of notification
FREEDOMS II[73]	Symptoms (not defined)	NR	NR	EDSS increase ⩾0.5 points, or increase ⩾1 on two functional scores or ⩾2 on one	NR	NR
GALA[94]	New or recurrent neurologic symptoms	≥ 48 hours	NR	EDSS increase ⩾0.5 points, or increase ⩾1 on two functional scores or ⩾2 on one	≥30 days	NR

Study Name	Symptoms	Symptom duration	Absence of	EDSS/neurological examination	Preceding stability period	Verification
GATE[95]	New or recurrent neurologic symptoms	≥ 24 hours	Fever or infection	New objective neurologic findings	NR	NR
GOLDEN[96]	*No definition provided*					
IFNB Multiple Sclerosis Study Group[97]	New or worsening neurologic symptom attributable to MS	≥ 24 hours	Fever	New objective neurologic findings	≥30 days	NR
IMPROVE[98]	*No definition provided*					
INCOMIN[99]	New or worsening neurologic symptom	≥ 24 hours	NR	⩾1 point increase in Kurtzke's functional system scale score	≥30 days	Investigating doctor ≤ 7 days of notification
Kappos 2011[100]	New or worsening neurologic symptom attributable to MS	≥ 24 hours	NR	EDSS increase ⩾0.5 points, or increase ⩾1 on two functional scores or ⩾2 on one	≥30 days	NR
MIST[72]	Neurologic symptoms requiring corticosteroids	≥ 24 hours	Fever, infection, or heat intolerance	NR	NR	Investigator not masked to treatment.
Multiple Sclerosis Collaborative Research Group[105]	New or worsening neurologic symptom	≥ 48 hours	NR	EDSS increase ⩾0.5 points, or increase ⩾1 on two functional scores or ⩾2 on one	≥30 days	Study physician
OPERA I[67]	New or worsening neurologic symptom attributable to MS	≥ 24 hours	Fever, infection, injury, or adverse reactions to medications	EDSS increase ⩾0.5 points, or increase ⩾1 on two functional scores or ⩾2 on one	≥30 days	NR
OPTIMUM[70]	New, worsening or recurrent neurologic symptom	≥ 24 hours	Fever or infection	Documented increase of EDSS score or its functional system scores	≥30 days	NR
PEGINTEGRITY[65]	*No definition provided*					

Study Name	Symptoms	Symptom duration	Absence of	EDSS/neurological examination	Preceding stability period	Verification
Ponesimod Phase II study Group[101]	New or worsening symptoms of MS	≥ 24 hours	Fever or infection	EDSS increase ⩾0.5 points, or increase ⩾1 on two functional scores or ⩾2 on one	≥30 days	Independent neurologist ≤ 7 days of notification
PRISMS[102]	New or worsening neurologic symptom attributable to MS	≥ 24 hours	NR	NR	≥30 days	NR
REGARD[103]	New or worsening neurologic symptom	≥ 48 hours	Fever	Change in KFS score.	NR	NR
REVEAL[78]	New or recurrent neurologic symptoms	≥ 24 hours	Fever	NR	≥30 days	NR
Saida 2012[104]	New, worsening or recurrent neurologic symptom	≥ 24 hours	NR	EDSS increase ⩾0.5 points, or increase ⩾1 on two functional scores or ⩾2 on one	≥30 days	NR
Saida 2017[79]	New or recurrent neurologic symptoms	≥ 24 hours	Fever or infection	NR	NR	NR
TRANSFORMS[75]	New, worsening or recurrent neurologic symptom	≥ 24 hours	NR	EDSS increase ⩾0.5 points, or increase ⩾1 on two functional scores or ⩾2 on one	≥30 days	Neurologist

Table 48 Annualised relapse rate analysis details

Study Name	Analysis details	Baseline characteristics adjusted for	Other factors adjusted for
ADVANCE[80]	Negative binomial regression model	EDSS score (<4 vs ≥4); relapse rate (number of relapses in 3 years before study entry divided by 3); age (<40 vs ≥40 years)	NR
AFFIRM[77]	Poisson regression	NR	NR
ANTELOPE[76]	Analysed descriptively – summarised as A: no. relapses per patient and overall, B: duration of follow-up time per patient and overall, A/B: the ratio of relapses per patient year	NR	NR
APOLITOS[69]	Negative binomial regression models	Treatment; region; number of Gd + T1 lesions (0 or ⩾1)	Offset to adjust for time in study
ASCLEPIOS I[68]	Negative binomial-regression model	NR	Offset to adjust for time spent in trial in years
ASCLEPIOS II[68]	Negative binomial-regression model	NR	Offset to adjust for variable study duration in years
ASSESS[81]	Negative binomial-regression model	EDSS score; no. gadolinium-enhancing T1 lesions; no. relapses in previous year before enrolment	Time in study (offset variable); number of confirmed relapses for each participant (response variable)
BEYOND[82]	Hazard ratios derived from generalised linear Poisson regression	NR	NR
Calabrese 2012[83]	Only statistical analysis information provided: Between-group differences were assessed using analysis of variance, followed by the Tukey test to account for multiple comparisons. Pearson chi-square was applied to test the effect of disease-modifying on the percentage of patients that developed new cortical inflammatory lesions compared with untreated patients.	NR	NR
CAMMS223[84]	Poisson regression	NR	NR
CARE-MS I[85]	Negative binomial regression	Geographic region	Robust variance estimation used as covariate

Study Name	Analysis details	Baseline characteristics adjusted for	Other factors adjusted for
CARE-MS II[71]	NA	NA	NA
CLARITY[86]	Proportion of relapse-free patients analysed with logistic-regression model that included study-group and region effects. Odds ratio and 95% confidence intervals estimated for each study group. Groups compared with approximate chi-square test on the basis of Wald statistics.	Region; study group	NR
CombiRx[87]	Cox proportional hazards model with Anderson Gill modification to handle repeated occurrences of relapses within a participant.	Baseline covariates that differed across treatment arms	NR
CONFIDENCE[88]	NA	NA	NA
CONFIRM[89]	Negative binomial regression model	age; region; no. relapses in the 12 months before study entry	
Copolymer 1 Multiple Sclerosis Study Group[90]	ANCOVA	EDSS score; sex; duration of disease (years); prior 2-year relapse rate	
Etemedifar 2006[91]	Comparison between groups made using one-way ANOVA and repeated-measures ANOVA over time; comparisons between, before, and after 24 months of treatment within each group made using paired Student's t-test. Comparisons between proportions made by using chi-square or Fisher's exact test. Results expressed as mean (SD) and P<0.05 considered statistically significant. All statistical tests were two-sided.	NR	NR
European/Canadian glatiramer acetate study group[92]	Continuous variables analysed with two-sample two-sided t test or Mann–Whitney test	NR	NR
EVIDENCE[93]	Poisson regression model	Treatment; centre	Offset variable for time on study
FREEDOMS[74]	Negative binomial regression model	EDSS score; study group; country; no. relapses within 2 years;	NR
FREEDOMS II[73]	Negative binomial regression model		NR

Study Name	Analysis details	Baseline characteristics adjusted for	Other factors adjusted for
		EDSS score; treatment; region; no. relapses within 2 years	
GALA[94]	Negative binomial regression model	EDSS score; treatment group; no. relapses in the previous 2 years; volume of T2 lesions; status of Gd-enhancing T1 activity; country or geographical region	Offset variable for patient's exposure to treatment
GATE[95]	Not formally tested but summarized per treatment group with point estimates and 95% CIs using an appropriate covariance model	Stratification variables included as covariates	NR
GOLDEN[96]	Continuous data were summarised by mean, standard deviation (SD), median, interquartile range, minimum and maximum, and 95% confidence limits (CLs), where applicable.	NR	NR
IMPROVE[98]	Poisson regression model	Treatment	Offset variable for time on study
INCOMIN[99]	Parametric or non-parametric tests, according to distribution of variables	NR	NR
IFNB Multiple Sclerosis Study Group[97]	Treatment-group differences were analysed using ANOVA based on ranked data. In display of group exacerbation rates, 95% CI were calculated using Poisson distribution based on no. observed exacerbations in each group. Survival curves were calculated with life-table methods for length of time before onset of first and second exacerbations. Data on patients were censored at time of withdrawal. Log-rank statistic was used to test comparability of the survival curves for each group.	ANOVA accounted for treatment group; study site; treatment group by study site	NR
Kappos 2011[100]	Poisson regression	Geographical region	Offset variable for exposure time in years
MIST[72]	NA	NA	NA
Multiple Sclerosis Collaborative Research Group[105]	Divided the total number of exacerbations during the first 104 weeks by the total person-years of exposure	NR	NR

Study Name	Analysis details	Baseline characteristics adjusted for	Other factors adjusted for
OPERA I[67]	Negative binomial model	EDSS score; geographic region	NR
OPERA II[67]	Negative binomial model	EDSS score; geographic region	NR
OPTIMUM[70]	Negative binomial regression model	NR	Offset variable for log time in study in years
PEGINTEGRITY[65]	Poisson regression model with robust error variance	EDSS score; age	NR
Ponesimod Phase II study Group[101]	Rate ratio provided; time to first confirmed relapse was analysed using the Kaplan–Meier method	NR	NR
PRISMS[102]	Generalised linear model (GLM) with a log link and variance proportional to the mean	NR	NR
REGARD[103]	Poisson regression model	Treatment; centre	Offset variable for time on study
REVEAL[78]	Negative binomial regression models	NR	NR
Saida 2012[104]	Logistic regression model	EDSS score; treatment; no. relapses in two years prior to study	NR
Saida 2017[79]	Poisson regression model	NR	NR
TRANSFORMS[75]	Logistic regression model	EDSS score; country; no. relapses in previous two years	

Table 49 Estimates of ARR for each study arm in the included studies (RRMS population)

Study Name	Intervention	Follow-up (months)	N	ARR (95% CI or SD)	RR (95% CI)	ROB
ADVANCE[80]	Peginterferon beta 1a SC125	12	512	0.26 (0.21, 0.32)	0.64 (0.50, 0.83)	Low
	Placebo		500	0.4 (0.33, 0.48)	1.0	
AFFIRM[77]	Natalizumab IV300	12	627	0.27 (0.21, 0.33)	0.35 (0.26, 0.47)	Low
	Placebo		315	0.78 (0.64, 0.94)	1.0	
	Natalizumab IV300	24	627	0.23 (0.19, 0.28)	0.32 (0.24, 0.41)	
	Placebo		315	0.73 (0.62, 0.87)	1.0	
ANTELOPE[76]	Natalizumab biosimilar	6	131	0.17 (NR)	1.55 (NR)	Low
	Natalizumab IV300		133	0.11 (NR)	1.0	
APOLITOS[69]	Ofatumumab SC20	6	43	0.26 (0.11, 0.63)	0.42 (0.14, 1.25)	Some concerns
	Placebo		21	0.63 (0.28, 1.43)	1.0	
ASCLEPIOS I[68]	Ofatumumab SC20	30	454	0.11 (0.09, 0.14)	0.49 (0.37, 0.65)	Low
	Teriflunomide O14		452	0.22 (0.18, 0.26)	1.0	
ASCLEPIOS II[68]	Ofatumumab SC20	30	469	0.1 (0.08, 0.13)	0.42 (0.31, 0.56)	Low
	Teriflunomide O14		469	0.25 (0.21, 0.3)	1.0	
ASSESS[81]	Fingolimod O0.5	12	345	0.15 (0.11, 0.21)	0.59 (0.37, 0.95)	High
	Glatiramer acetate SC20		324	0.26 (0.2, 0.34)	1.0	
BEYOND[82]	Glatiramer acetate SC20	24	448	0.34 (NR)	0.94 (NR)	Some concerns
	Interferon beta 1b IM 250		897	0.36 (NR)	1.0	
Calabrese 2012[83]	Glatiramer acetate SC40	24	48	0.5 (0.39, 0.61)	1.25 (0.75, 2.07)	Some concerns
	Interferon beta 1a IM30		47	0.5 (0.33, 0.67)	1.25 (0.70, 2.22)	
	Interferon beta 1a SC44		46	0.4 (0.23, 0.57)	1.0	
CAMMS223[84]	Alemtuzumab IV12	36	112	0.11 (0.08, 0.16)	0.33 (0.2, 0.55)	High
	Interferon beta 1a SC44		111	0.36 (0.29, 0.44)	1.0	
CARE-MS I[85]	Alemtuzumab IV12	24	376	0.18 (0.13, 0.23)	0.45 (0.32, 0.63)	High
	Interferon beta 1a SC44		187	0.39 (0.29, 0.53)	1.0	
CLARITY[86]	Cladribine O3.5	24	433	0.14 (0.12, 0.17)	0.42 (0.34, 0.53)	Some concerns
	Placebo		437	0.33 (0.29, 0.38)	1.0	
CombiRx[87]	Glatiramer acetate SC20	36	259	0.23 (NR)	0.72 (NR)	Low
	Interferon beta 1a IM30		250	0.32 (NR)	1.0	
CONFIRM[89]	Glatiramer acetate SC20	24	350	0.29 (0.23, 0.35)	0.73 (0.54, 0.97)	Some concerns
	Placebo		363	0.4 (0.33, 0.49)	1.0	
Copolymer 1 Multiple Sclerosis Study Group[90]	Glatiramer acetate SC20	24	125	0.59 (NR)	0.7 (NR)	Some concerns
	Placebo		126	0.84 (NR)	1.0	
Etemedifar 2006[91]	Interferon beta 1a IM30	24	30	0.6 (NR)	2.0 (NR)	Some concerns
	Interferon beta 1b IM 250		30	0.35 (NR)	1.17 (NR)	
	Interferon beta 1a SC44		30	0.3 (NR)	1.0	
European/Canadian glatiramer acetate study group[92]	Glatiramer acetate SC20	9	119	0.81 (NR)	0.67 (NR)	Some concerns
	Placebo		120	1.21 (NR)	1.0	
EVIDENCE[93]	Interferon beta 1a IM30	16	338	0.65 (NR)	1.2(NR)	Some concerns
	Interferon beta 1a SC44		339	0.54 (NR)	1.0	
FREEDOMS[74]	Fingolimod O0.5	24	425	0.18 (0.15, 0.22)	0.45 (0.35, 0.58)	Low
	Placebo		418	0.4 (0.34, 0.47)	1.0	
FREEDOMS II[73]	Fingolimod O0.5	24	358	0.21 (0.17, 0.25)	0.52 (0.4, 0.66)	High
	Placebo		355	0.4 (0.34, 0.48)	1.0	

Study Name	Intervention	Follow-up (months)	N	ARR (95% CI or SD)	RR (95% CI)	ROB
GALA[94]	Glatiramer acetate SC40	12	943	0.33 (0.28, 0.39)	0.66 (0.54, 0.8)	Low
	Placebo		461	0.51 (0.42, 0.61)	1.0	
GATE[95]	Glatiramer acetate SC20	9	357	0.4 (0.26, 0.62)	1.05 (0.52, 2.12)	Low
	Placebo		84	0.38 (0.22, 0.66)	1.0	
GOLDEN[96]	Fingolimod O0.5	18	104	0.12 (NR)	0.31(NR)	High
	Interferon beta 1b IM 250		47	0.39 (NR)	1.0	
IFNB Multiple Sclerosis Study Group[97]	Interferon beta 1b IM 250	21.6	115	0.84 (0.72, 0.97)	0.66 (0.55, 0.80)	Some concerns
	Placebo	22.4	112	1.27 (1.12, 1.43)	1	
	Interferon beta 1b IM 250	36	124	0.84 (NR)	0.69 (NR)	
	Placebo		123	1.21 (NR)	1.0	
IMPROVE[98]	Interferon beta 1a SC44	4	120	0.14 (0.09, 0.23)	0.43 (0.23, 0.82)	Some concerns
	Placebo		60	0.33 (0.22, 0.52)	1.0	
INCOMIN[99]	Interferon beta 1b IM 250	24	96	0.5 (0.7)	0.71(NR)	High
	Interferon beta 1a IM30		92	0.7 (0.9)	1.0	
Kappos 2011[100]	Interferon beta 1a IM30	6	54	0.36 (0.22, 0.6)	0.56 (0.30, 1.06)	Low
	Ocrelizumab IV600		55	0.13 (0.03, 0.29)	0.20 (0.06, 0.67)	
	Placebo		54	0.64 (0.43, 0.94)	1.0	
Multiple Sclerosis Collaborative Research Group[105]	Interferon beta 1a IM30	24	158	0.67 (NR)	0.82(NR)	Some concerns
	Placebo	24	143	0.82 (NR)	1.0	
OPERA I[67]	Ocrelizumab IV600	24	410	0.16 (0.12, 0.2)	0.54 (0.4, 0.72)	Low
	Interferon beta 1a SC44		411	0.29 (0.24, 0.36)	1.0	
OPERA II[67]	Ocrelizumab IV600	24	417	0.16 (0.12, 0.2)	0.53 (0.4, 0.71)	Low
	Interferon beta 1a SC44		418	0.29 (0.23, 0.36)	1.0	
OPTIMUM[70]	Ponesimod O20	27	567	0.2 (0.17, 0.23)	0.69 (0.54, 0.9)	Low
	Teriflunomide O14		566	0.29 (0.25, 0.33)	1.0	
PEGINTEGRITY[65]	Interferon beta 1a IM30	24	83	0.12 (0.05, 0.27)	0.54 (0.23, 1.29)	High
	Peginterferon beta 1a SC125		84	0.06 (0.03, 0.14)	1.0	
Ponesimod Phase II study Group[101]	Ponesimod O20	6	114	0.42 (0.27, 0.65)	0.79 (0.44, 1.43)	Low
	Placebo		121	0.53 (0.36, 0.77)	1.0	
PRISMS[102]	Interferon beta 1a SC22	12	189	1.01 (0.86, 1.19)	0.68 (0.55, 0.84)	Some concerns
	Interferon beta 1a SC44		184	0.92 (0.78, 1.09)	0.62 (0.50, 0.77)	
	Placebo		187	1.49 (1.29, 1.72)	1.0	
	Interferon beta 1a SC22	24	189	0.91 (NR)	0.71 (NR)	
	Interferon beta 1a SC44		184	0.87 (NR)	0.68 (NR)	
	Placebo		187	1.28 (NR)	1.0	
REGARD[103]	Glatiramer acetate SC20	24	378	0.29 (NR)	0.97(NR)	Some concerns
	Interferon beta 1a SC44		386	0.3 (NR)	1.0	
REVEAL[78]	Natalizumab IV300	9	54	0.02 (0.01, 0.13)	0.09 (0.01, 0.72)	Some concerns
	Fingolimod O0.5		54	0.2 (0.11, 0.37)	1.0	
Saida 2012[104]	Fingolimod O0.5	6	57	0.5 (0.29, 0.87)	0.51 (0.26, 0.99)	Low
	Placebo		57	0.99 (0.67, 1.45)	1.0	
Saida 2017[79]	Natalizumab IV300	6	47	0.53 (0.29, 0.99)	0.31 (0.15, 0.62)	Low
	Placebo		47	1.73 (1.22, 2.45)	1.0	
TRANSFORMS[75]	Fingolimod O0.5	12	429	0.16 (0.12, 0.21)	0.48 (0.34, 0.70)	Low
	Interferon beta 1a IM30		431	0.33 (0.26, 0.42)	1.0	

For RR: light grey shading indicates RR estimates reported by the included studies; darker grey shading indicates studies that where RR and 95% CI were calculated from reported ARR and 95% CI for studies arms; unshaded indicates studies that did not report CIs.

Table 50 Estimates of ARR for each study arm in the included studies (HARRMS population)

Study Name	Intervention	Follow-up (months)	N	ARR (95% CI or SD)	ROB
CARE-MS II[71]	Interferon beta 1a SC44	24	202	0.52 (0.41, 0.66)	High
	Alemtuzumab IV12	24	426	0.26 (0.21, 0.33)	
CLARITY[86]	Placebo	24	56	0.44 (0.33, 0.6)	Some concerns
	Cladribine O3.5	24	46	0.25 (0.16, 0.39)	
FREEDOMS 1/II[108]	Placebo	24	257	0.46 (0.39, 0.55)	High
	Fingolimod O0.5	24	249	0.24 (0.19, 0.3)	
OPERA I/II[67]	Ocrelizumab IV600	24	143	0.099 (NR, NR)	Low
	Interferon beta 1a SC44	24	140	0.313 (NR, NR)	
Saida 2017[79]	Natalizumab IV300	6	47	0.53 (0.29, 0.99)	Low
	Placebo		47	1.73 (1.22, 2.45)	
TRANSFORMS[75]	Fingolimod O0.5	12	189	0.252 (NR, NR)	Low
	Interferon beta 1a IM30	12	191	0.506 (NR, NR)	

Disease progression

Table 51 CDP definitions and estimates of proportion of patients with CDP3 and CDP6 for each study arm in the included trials and Hazard Ratios (HR) comparing time to CDP3 and CDP6 between arms (RRMS population)

Study Name	CDP definition based on baseline EDSS scores			Intervention	Follow-up (mths)	CDP3		CDP6		ROB
	EDSS increase 0.5 point	EDSS increase 1 point	EDSS increase 1.5 pts			n/N (%)	HR (95% CI)	n/N (%)	HR (95% CI)	
ADVANCE[80]	NA	≥1	0	Peginterferon beta 1a SC125	12	31/512(6)	0.62 (0.4, 0.97)	NR/512 (NR)	0.46 (0.26, 0.81)	Low
				Placebo	12	50/500(10)	1.0	NR/500 (NR)	1.0	
AFFIRM[77]	NA	≥1	0	Natalizumab IV300	24	107/627(17)	0.58 (0.43, 0.77)	69/627 (11)	0.46 (0.33, 0.64)	Some concerns
				Placebo	24	91/315(29)	1.0	72/315 (23)	1.0	
ASCLEPIOS I[68]	>5.0	1-5	0	Ofatumumab SC20	24	45/465(10)	0.65 (0.45, 0.96)	35/465 (8)	0.61 (0.4, 0.93)	Low
				Teriflunomide O14	24	63/459(14)	1.0	53/459 (12)	1.0	
ASCLEPIOS II[68]	>5.0	1-5	0	Ofatumumab SC20	24	43/479(9)	0.66 (0.45, 0.97)	36/479 (8)	0.76 (0.49, 1.17)	Low
				Teriflunomide O14	24	62/472(13)	1.0	46/472 (10)	1.0	
BEYOND[82]	NA	All	NA	Interferon beta 1b IM 250	24	244/897(27)	NR	NR		Some concerns
				Glatiramer acetate SC20	24	92/448(21)				
CAMMS223[84]	NA	≥1	0	Alemtuzumab IV12	36	12/112(11)	0.42 (0.23, 0.77)	8/112 (7)	0.25 (0.11, 0.57)	High
				Interferon beta 1a SC44	36	16/111(14)	1.0	24/111 (22)	1.0	
CARE-MS I[85]	NA	≥1	0	Alemtuzumab IV12	24	NR		30/376 (8)	0.7 (0.4, 1.23)	High
				Interferon beta 1a SC44	24			20/187 (11)	1.0	
CLARITY[86]	NA	≥1	0	Cladribine O3.5	24	62/433(14)	0.67 (0.48, 0.93)	168/392 (43)	NR	Some concerns
				Placebo	24	90/437(21)	1.0	164/374 (44)		
CombiRx[87]	>5.0	0 to 5	NA	Interferon beta 1a IM30	36	NR		52/241 (22)	NR	Low
				Glatiramer acetate SC20	36			61/246 (25)		
CONFIRM[89]	NA	≥1	0	Glatiramer acetate SC20	24	16/350(5)	0.93 (0.63, 1.37)	NR		Some concerns
				Placebo	24	17/363(5)	1.0			
	NA	All	NA	Glatiramer acetate SC20	24	27/125(22)	NR	NR		

Study Name	CDP definition based on baseline EDSS scores			Intervention	Follow-up (mths)	CDP3		CDP6		ROB
	EDSS increase 0.5 point	EDSS increase 1 point	EDSS increase 1.5 pts			n/N (%)	HR (95% CI)	n/N (%)	HR (95% CI)	
Copolymer 1 Multiple Sclerosis Study Group[90]				Placebo	24	31/126(25)				Some concerns
EVIDENCE[93]	NA	≥1	0	Interferon beta 1a SC44	6	43/339(13)	0.87 (0.58, 1.31)	20/339 (6)	0.7 (0.39, 1.25)	Some concerns
				Interferon beta 1a IM30	6	49/338(14)	NR	30/338 (9)	1.0	
FREEDOMS[74]	>5.0	≤5	NA	Fingolimod O0.5	24	NR/425 (NR)	0.70 (0.52, 0.96)	NR/425 (NR)	0.63 (0.44, 0.90)	Low
				Placebo	24	NR/418 (NR)	1.0	NR/418 (NR)	1.0	
FREEDOMS II[73]	>5.0	≤5	NA	Fingolimod O0.5	24	91/358(25)	0.83 (0.61, 1.12)	49/358 (14)	0.72 (0.48, 1.07)	High
				Placebo	24	103/355(29)	1.0	63/355 (18)	1.0	
INCOMIN[99]	NA	All	NA	Interferon beta 1b IM 250	24	NR		13/96 (14)	0.44 (0.25, 0.8)	High
				Interferon beta 1a IM30	24			28/92 (30)	1.0	
Multiple Sclerosis Collaborative Research Group[105]	NA	All	NA	Interferon beta 1a IM30		NR		18/85 (21)	NR	Some concerns
				Placebo				29/87 (33)		
OPERA I[67]	> 5.5	≤5.5	NA	Ocrelizumab IV600	24	31/410(8)	0.57 (0.37, 0.9)	24/410 (6)	0.57 (0.34, 0.95)	Low
				Interferon beta 1a SC44	24	50/411(12)	1.0	39/411 (9)	1.0	
OPERA II[67]	> 5.5	≤5.5	NA	Ocrelizumab IV600	24	44/417(11)	0.63 (0.42, 0.92)	33/417 (8)	0.63 (0.4, 0.98)	Low
				Interferon beta 1a SC44	24	63/418(15)	1.0	48/418(11)	1.0	
OPTIMUM[70]	> 5.5	1 to 5.5	0	Ponesimod O20	27	57/567(10)	0.83 (0.58, 1.18)	46/567(8)	0.84 (0.57, 1.24)	Low
				Teriflunomide O14	27	70/566(12)	1.0	56/566(10)	1.0	
PEGINTEGRITY[65]	> 5.5	1 to 5.5	0	Peginterferon beta 1a SC125	24	1/78(1)	0.58 (0.05, 6.47)	NR		High
				Interferon beta 1a IM30	24	2/81(2)	1.0			
PRISMS[102]	> 5.5	≤5.5	NA	Interferon beta 1a SC22	12	NR/189	0.55 (0.35, 0.85)	NR		Some concerns
				Interferon beta 1a SC44	12	NR/184	0.62 (0.41, 0.95)			
				Placebo	12	NR/187	1.0			
REGARD[103]	≥5	0.5-4.5	0	Glatiramer acetate SC20	24	NR		33/378(9)	NR	Some concerns
				Interferon beta 1a SC44	24			45/386(12)		

Study Name	CDP definition based on baseline EDSS scores			Intervention	Follow-up (mths)	CDP3		CDP6		ROB
	EDSS increase 0.5 point	EDSS increase 1 point	EDSS increase 1.5 pts			n/N (%)	HR (95% CI)	n/N (%)	HR (95% CI)	
TRANSFORMS[75]	>5.0	≤5	NA	Interferon beta 1a IM30	12	34/431(8)	NR	NR		Low
				Fingolimod O0.5	12	36/429(8%)				

Table 52 CDP definitions and estimates of proportion of patients with CDP3 and CDP6 for each study arm in the included trials and Hazard Ratios (HR) comparing time to CDP3 and CDP6 between arms (HARRMS population)

Study Name	CDP definition based on baseline EDSS scores			Intervention	Follow-up (mths)	CDP3		CDP6		ROB
	EDSS increase 0.5 point	EDSS increase 1 point	EDSS increase 1.5 pts			n/N (%)	HR (95% CI)	n/N (%)	HR (95% CI)	
CARE-MS II[71]	NA	≥2	NA	Alemtuzumab IV12	24	NR		54/426(13)	0.58 (0.38, 0.87)	High
				Interferon beta 1a SC44				40/202(20)		
CLARITY[86]	NA	≥1	0	Cladribine O3.5	24	NR/46	0.25 (0.07, 0.89)	NR/46	0.20 (0.04, 0.91)	Some concerns
				Placebo		NR/56	1.0	NR/56	1.0	
FREEDOMS 1/II[108]	>5.0	≤5	NA	Fingolimod O0.5	24	NR		26/248 (10)	0.50 (0.34, 0.90)	High
				Placebo				43/257 (17)	1.0	
MIST[72]	NA	All	NA	AHSCT	34	NR		3/52 (6)	0.07 (0.02, 0.24)	High
				iDMT				34/51 (67)	1.0	
OPERA I/II[67]	> 5.5	≤5.5	NA	Ocrelizumab IV600	24	12/143 (8)	0.47 (0.23, 0.95)	10/143 (7)	0.50 (0.23, 1.09)	Low
				Interferon beta 1a SC44		22/140 (16)	1.0	17/140 (12)	1.0	

MRI outcomes

Table 53 Definitions and estimates of proportion of patients with lesions on MRI for each study arm in the included trials (RRMS population)

Study Name	Gd+ lesion definition	T2 lesions definition	Follow-up (months)	Intervention	% Gd+ lesions	% T2 lesions	ROB
AFFIRM[77]	Any Gd+ lesions	New or enlarging T2 hyperintense lesions	24	Natalizumab IV300	19/627 (3%)	267/627 (43%)	Low
				Placebo	88/315 (28%)	269/315 (85%)	
			12	Natalizumab IV300	22/627 (4%)	245/627 (39%)	
				Placebo	102/315 (32%)	243/315 (77%)	
ANTELOPE[76]	New Gd+ lesions	New or enlarging T2 lesion	6	Natalizumab biosimilar	17/126 (13%)	51/126 (40%)	Low
				Natalizumab IV300	22/127 (17%)	55/127 (43%)	
ASSESS[81]	Any Gd+ lesions	New or enlarging T2 lesions	12	Fingolimod O0.5	41/302 (14%)	147/303 (49%)	High
				Glatiramer acetate SC20	70/272 (26%)	176/272 (65%)	
CARE-MS I[85]	Any Gd+ lesions	New or enlarging T2 hyperintense lesions	24	Alemtuzumab IV12	26/366 (7%)	176/363 (48%)	High
				Interferon beta 1a SC44	34/178 (19%)	99/172 (58%)	
CLARITY[86]	Any Gd+ lesion	Active T2 lesions	24	Cladribine O3.5	54/422 (13%)	148/422 (35%)	High
				Placebo	223/424 (53%)	284/424 (67%)	
CombiRx[87]	And Gd+ lesions	NR	36	Interferon beta 1a IM30	25/187 (13%)	NR	Some concerns
				Glatiramer acetate SC20	33/215 (15%)	NR	
EVIDENCE[93]	Any Gd+ lesions	New or enlarging T2 hyperintense lesions	6	Interferon beta 1a SC44	270/325 (83%)	265/325 (82%)	Some concerns
				Interferon beta 1a IM30	287/325 (88%)	282/325 (87%)	
FREEDOMS[74]	Any Gd+ lesions	New or enlarging T2 lesion	24	Fingolimod O0.5	38/369 (10%)	183/370 (49%)	Some concerns
				Placebo	116/332 (35%)	267/339 (79%)	
FREEDOMS II[73]	Any Gd+ lesions	New hyperintense T2 lesions	24	Fingolimod O0.5	35/269 (13%)	131/264 (50%)	High
				Placebo	89/256 (35%)	186/251 (74%)	
GATE[95]	Any Gd+ lesions	New hyperintense T2 lesions	9	Glatiramer acetate SC20	193/335 (58%)	NR	Low
				Placebo	59/82 (72%)	NR	
IMPROVE[98]	New Gd+ lesions	New T2 lesions	4	Interferon beta 1a SC44	47/120 (39%)	27/120 (23%)	Some concerns
				Placebo	48/60 (80%)	30/60 (50%)	

Study Name	Gd+ lesion definition	T2 lesions definition	Follow-up (months)	Intervention	% Gd+ lesions	% T2 lesions	ROB
INCOMIN[99]	Any Gd+ lesions	New T2 lesions	12	Interferon beta 1b IM 250	7/76 (9%)	53/76 (70%)	High
				Interferon beta 1a IM30	16/73 (22%)	33/73 (45%)	
			24	Interferon beta 1b IM 250	18/76 (24%)	34/76 (45%)	
				Interferon beta 1a IM30	37/73 (51%)	54/73 (74%)	
Multiple Sclerosis Collaborative Research Group[105]	Any Gd+ lesions	NR	12	Interferon beta 1a IM30	40/134 (30%)	NR	Some concerns
				Placebo	52/123 (42%)	NR	
OPERA I[67]	Any Gd+ lesions	New or enlarging T2 lesions	24	Ocrelizumab IV600	21/410 (5%)	155/410 (38%)	Low
				Interferon beta 1a SC44	112/411 (27%)	249/411 (61%)	
OPERA II[67]	Any Gd+ lesions	New or enlarging T2 lesions	24	Ocrelizumab IV600	20/417 (5%)	153/417 (37%)	Low
				Interferon beta 1a SC44	139/418 (33%)	255/418 (61%)	
PRISMS[102]	NR	Active T2 lesions	12	Interferon beta 1a SC44	NR	66/182 (36%)	Some concerns
				Interferon beta 1a SC22	NR	94/185 (51%)	
				Placebo	NR	136/184 (74%)	
			24	Interferon beta 1a SC44	NR	126/182 (69%)	
				Interferon beta 1a SC22	NR	150/185 (81%)	
				Placebo	NR	169/184 (92%)	
REGARD[103]	Any Gd+ lesions	Active T2 lesions	24	Interferon beta 1a SC44	44/230 (19%)	137/230 (60%)	Some concerns
				Glatiramer acetate SC20	76/230 (33%)	144/230 (63%)	
REVEAL[78]	New Gd+ lesions	New/newly enlarging T2 lesions	6	Natalizumab IV300	16/47 (34%)	6/15 (40%)	Some concerns
				Fingolimod O0.5	24/45 (53%)	10/16 (63%)	
Saida 2012[104]	Any Gd+ lesions	New or enlarging T2 lesions	6	Fingolimod O0.5	11/45 (24%)	17/48 (35%)	Some concerns
				Placebo	23/50 (46%)	32/50 (64%)	
TRANSFORMS[75]	Any Gd+ lesions	New or enlarged T2-weighted hyperintense lesions	12	Fingolimod O0.5	37/374 (10%)	168/372 (45%)	Some concerns
				Interferon beta 1a IM30	68/354 (19%)	196/361 (54%)	

Table 54 Definitions and estimates of proportion of patients with lesions on MRI for each study arm in the included trials (HARRMS population)

Study Name	Gd+ lesion definition	T2 lesions definition	Follow-up (months)	Intervention	% Gd+ lesions	% T2 lesions	ROB
CARE-MS II[71]	Any Gd+ lesions	New or enlarging T2-hyperintense lesions	24	Alemtuzumab IV12	38/410 (9%)	186/403 (46%)	High
				Interferon beta 1a SC44	44/190 (23%)	127/187 (68%)	

Adverse events

Table 55 Proportion of participants reporting each of the safety outcomes of interest (RRMS population)

Study Name	Follow-up (Months)	Intervention	Number of patients experiencing each type of AE/total number of patients (% of patients)				ROB
			Any AEs	SAEs	AEs leading to treatment discontinuation	TRAE	
ADVANCE[80]	12	Placebo	417/500 (83%)	76/500 (15%)	7/500 (1%)	266/500 (53%)	Low
		Peginterferon beta 1a SC125	481/512 (94%)	5/512 (1%)	25/512 (5%)	459/512 (90%)	
AFFIRM[77]	24	Placebo	300/312 (96%)	75/312 (24%)	12/312 (4%)	NR	Low
		Natalizumab IV300	596/627 (95%)	119/627 (19%)	38/627 (6%)	NR	
ANTELOPE[76]	12	Natalizumab biosimilar	85/131 (65%)	NR	8/131 (6%)	31/131 (24%)	Low
		Natalizumab IV300	71/103 (69%)	NR	3/103 (3%)	22/103 (21%)	
APOLITOS[69]	6	Placebo	NR	0/21 (0%)	NR	17/21 (81%)	Some concerns
		Ofatumumab SC20	NR	1/43 (2%)	NR	30/43 (70%)	
ASCLEPIOS I[68]	30	Teriflunomide O14	380/462 (82%)	38/462 (8%)	24/462 (5%)	NR	Low
		Ofatumumab SC20	382/465 (82%)	48/465 (10%)	27/465 (6%)	NR	
ASCLEPIOS II[68]	30	Teriflunomide O14	408/474 (86%)	36/474 (8%)	25/474 (5%)	NR	Low
		Ofatumumab SC20	409/481 (85%)	38/481 (8%)	27/481 (6%)	NR	
ASSESS[81]	12	Fingolimod O0.5	312/345 (90%)	25/345 (7%)	32/345 (9%)	NR	High
		Glatiramer acetate SC20	283/324 (87%)	20/324 (6%)	45/324 (14%)	NR	
BEYOND[82]	Up to 42 months	Interferon beta 1b IM 250	NR	100/888 (11%)	13/888 (1%)	NR	Some concerns
		Glatiramer acetate SC20	NR	57/445 (13%)	8/445 (2%)	NR	
Calabrese 2012[83]	Did not report safety data						
CAMMS223[84]	36	Interferon beta 1a SC44	107/107 (100%)	24/107 (22%)	13/107 (12%)	NR	High
		Alemtuzumab IV12	108/108 (100%)	24/108 (22%)	2/108 (2%)	NR	
CARE-MS I[85]	24	Interferon beta 1a SC44	172/187 (92%)	27/187 (14%)	11/187 (6%)	NR	High
		Alemtuzumab IV12	361/376 (96%)	69/376 (18%)	5/376 (1%)	NR	
CLARITY[86]	24	Cladribine O3.5	347/430 (81%)	NR	15/430 (3%)	NR	Low

Study Name	Follow-up (Months)	Intervention	Number of patients experiencing each type of AE/total number of patients (% of patients)				ROB
			Any AEs	SAEs	AEs leading to treatment discontinuation	TRAE	
		Placebo	319/435 (73%)	NR	9/435 (2%)	NR	
CombiRx[87]	36	Glatiramer acetate SC20	NR	30/259 (12%)	NR	NR	Low
		Interferon beta 1a IM30	NR	38/250 (15%)	NR	NR	
CONFIDENCE[88]	6	Glatiramer acetate SC20	219/427 (51%)	8/427 (2%)	18/427 (4%)	142/427 (33%)	Some concerns
		Glatiramer acetate SC40	231/430 (54%)	13/430 (3%)	13/430 (3%)	143/430 (33%)	
CONFIRM[89]	24	Glatiramer acetate SC20	334/351 (95%)	60/351 (17%)	NR	NR	Low
		Placebo	333/363 (92%)	79/363 (22%)	NR	NR	
Copolymer 1 Multiple Sclerosis Study Group[90]	24	Placebo	NR	NR	1/126 (1%)	NR	Some concerns
		Glatiramer acetate SC20	NR	NR	5/125 (4%)	NR	
Etemedifar 2006[91]	Did not report safety data						
European/Canadian glatiramer acetate study group[92]	9	Placebo	NR	6/120 (5%)	2/120 (2%)	NR	Some concerns
		Glatiramer acetate SC20	NR	10/119 (8%)	3/119 (3%)	NR	
EVIDENCE[93]	6	Interferon beta 1a IM30	NR	18/338 (5%)	14/338 (4%)	NR	Some concerns
		Interferon beta 1a SC44	NR	21/339 (6%)	16/339 (5%)	NR	
	16	Interferon beta 1a IM30	NR	NR	18/338 (5%)	NR	
		Interferon beta 1a SC44	NR	NR	19/339 (6%)	NR	
FREEDOMS[74]	24	Placebo	387/418 (93%)	56/418 (13%)	32/418 (8%)	NR	Low
		Fingolimod O0.5	401/425 (94%)	43/425 (10%)	32/425 (8%)	NR	
FREEDOMS II[73]	24	Placebo	343/355 (97%)	45/355 (13%)	37/355 (10%)	NR	Low
		Fingolimod O0.5	350/358 (98%)	53/358 (15%)	66/358 (18%)	NR	
GALA[94]	12	Glatiramer acetate SC40	680/943 (72%)*	42/943 (4%)	29/943 (3%)	NR	Low
		Placebo	284/461 (62%)*	21/461 (5%)	6/461 (1%)	NR	
GATE[95]	9	Placebo	47/84 (56%)	2/84 (2%)	2/84 (2%)	NR	Low
		Glatiramer acetate SC20	194/357 (54%)	17/357 (5%)	4/357 (1%)	NR	
GOLDEN[96]	18	Interferon beta 1b IM 250	28/47 (60%)	1/47 (2%)	3/47 (6%)	NR	High

Study Name	Follow-up (Months)	Intervention	Number of patients experiencing each type of AE/total number of patients (% of patients)				ROB
			Any AEs	SAEs	AEs leading to treatment discontinuation	TRAE	
		Fingolimod O0.5	83/104 (80%)	9/104 (9%)	5/104 (5%)	NR	
IMPROVE[98]	4	Placebo	NR	3/60 (5%)	NR	NR	Some concerns
		Interferon beta 1a SC44	NR	4/120 (3%)	NR	NR	
INCOMIN[99]	Did not report any safety outcomes of interest; reported data for specific AEs only						
IFNB Multiple Sclerosis Study Group[97]	24	Placebo	NR	NR	1/123 (1%)	NR	Some concerns
		Interferon beta 1b IM 250	NR	NR	10/124 (8%)	NR	
Kappos 2011[100]	6	Ocrelizumab IV600	34/55 (62%)	1/55 (2%)	2/55 (4%)	17/55 (31%)	Low
		Interferon beta 1a IM30	30/54 (56%)	2/54 (4%)	1/54 (2%)	19/54 (35%)	
		Placebo	38/54 (70%)	2/54 (4%)	0/54 (0%)	25/54 (46%)	
Multiple Sclerosis Collaborative Research Group[105]	24	Placebo	NR	NR	2/143 (1%)	NR	Some concerns
		Interferon beta 1a IM30	NR	NR	7/158 (4%)	NR	
OPERA I[67]	24	Ocrelizumab IV600	327/408 (80%)	28/408 (7%)	NR	NR	Low
		Interferon beta 1a SC44	331/409 (81%)	32/409 (8%)	NR	NR	
OPERA II[67]	24	Ocrelizumab IV600	360/417 (86%)	29/417 (7%)	NR	NR	Low
		Interferon beta 1a SC44	357/417 (86%)	40/417 (10%)	NR	NR	
OPTIMUM[70]	27	Teriflunomide O14	499/566 (88%)	46/566 (8%)	34/566 (6%)	NR	Low
		Ponesimod O20	502/565 (89%)	49/565 (9%)	49/565 (9%)	NR	
PEGINTEGRITY[65]	24	Peginterferon beta 1a SC125	84/84 (100%)	2/84 (2%)	NR	63/84 (75%)	High
		Interferon beta 1a IM30	83/83 (100%)	2/83 (2%)	NR	66/83 (80%)	
Ponesimod Phase II study Group[101]	6	Placebo	90/121 (74%)	5/121 (4%)	NR	NR	Low
		Ponesimod O20	88/114 (77%)	7/114 (6%)	NR	NR	
PRISMS[102]	Did not report any safety outcomes of interest; reported data for specific AEs only						
REGARD[103]	24	Glatiramer acetate SC20	1917/375 (511%)*	27/375 (7%)	19/375 (5%)	618/375 (165%)*	Some concerns

Study Name	Follow-up (Months)	Intervention	Number of patients experiencing each type of AE/total number of patients (% of patients)				ROB
			Any AEs	SAEs	AEs leading to treatment discontinuation	TRAE	
		Interferon beta 1a SC44	1880/381 (493%)*	29/381 (8%)	23/381 (6%)	632/381 (166%)*	
REVEAL[78]	6	Natalizumab IV300	NR	0/54 (0%)	1/54 (2%)	23/54 (43%)	Some concerns
		Fingolimod O0.5	NR	2/54 (4%)	3/54 (6%)	32/54 (59%)	
Saida 2012[104]	6	Placebo	45/57 (79%)	3/57 (5%)	3/57 (5%)	NR	Low
		Fingolimod O0.5	52/57 (91%)	5/57 (9%)	6/57 (11%)	NR	
Saida 2017[79]	6	Natalizumab IV300	34/47 (72%)	7/47 (15%)	0/47 (0%)	NR	Low
		Placebo	41/47 (87%)	11/47 (23%)	1/47 (2%)	NR	
TRANSFORMS[75]	12	Interferon beta 1a IM30	395/431 (92%)	25/431 (6%)	16/431 (4%)	NR	Low
		Fingolimod O0.5	369/429 (86%)	30/429 (7%)	24/429 (6%)	NR	

*Studies reported total number of events rather than number of patients with events

Table 56 Proportion of participants reporting each of the safety outcomes of interest (HARRMS population)

Study Name	Follow-up (Months)	Intervention	Number of patients experiencing each type of AE/total number of patients (% of patients)				ROB
			Any AEs	SAEs	AEs leading to treatment discontinuation	TRAE	
CARE-MS II[71]	24	Alemtuzumab IV12	428/435 (98%)	138/435 (32%)	14/435 (3%)	NR	High
		Interferon beta 1a SC44	191/202 (95%)	77/202 (38%)	15/202 (7%)	NR	
Saida 2017[79]	6	Natalizumab IV300	34/47 (72%)	7/47 (15%)	0/47 (0%)	NR	Low
		Placebo	41/47 (87%)	11/47 (23%)	1/47 (2%)	NR	

HRQoL

Table 57 Quality of Life data (RRMS population)

Study Name	Intervention	Timepoint	EQ-5D			SF-36			Other measure reported	ROB
			N	Mean utility score (SD)	Mean VAS (SD)	Compo nent	N	mean (SD or 95% CI)		
CLARITY[86]	Cladribine O3.5	Baseline	353	0.72 (0.20)	70.22 (19.1)	NR			NR	High
	Placebo		349	0.72 (0.19)	68.9 (21.1)					
	Cladribine O3.5	12	338	0.72 (0.22)	70.7 (18.1)					
	Placebo		318	0.70 (0.22)	67.7 (20.6)					
	Cladribine O3.5	24	345	0.73 (0.22)	71.9 (19.4)					
	Placebo		338	0.66 (0.26)	66.3 (22.6)					
FREEDOMS II[73]	Fingolimod O0.5	24	358	Mean change from baseline = –0·016 (0·20)	Mean change from baseline 0·04 (15·0)	NR			NR	High
	Placebo		355	Mean change from baseline= –0·004 (0·23); p=0.328	–0·67 (15·21); p=0·143					
ADVANCE[80]	Peginterferon beta 1a SC125	11	512	No significant change from baseline (results not reported)		MCS & PCS	512	No significant change from baseline (results not reported)	MSIS-29	Low
	Placebo	11	500			MCS	500			
CARE-MS I[85]	Alemtuzumab IV12	24	376	No difference between groups (p>0.05)		MCS & PCS	376	No difference between groups (p>0.05)	FAMS	High
	Interferon beta 1a SC44		187				187			
CONFIRM[89]	Glatiramer acetate SC20	24	338	No difference between groups (p>0.05)	No difference between groups (p>0.05)	MCS	330	Greater improvement with GA than placebo (p<0.05)	NR	Low for VAS some concerns for other QoL data
	Placebo		349				344			

Study Name	Intervention	Timepoint	EQ-5D			SF-36			Other measure reported	ROB
			N	Mean utility score (SD)	Mean VAS (SD)	Component	N	mean (SD or 95% CI)		
	Glatiramer acetate SC20		NA			PCS	330	No difference between groups (p>0.05)		
	Placebo						344			
AFFIRM[77]	Natalizumab IV300	24M	NR			MCS	536	2.00 (10.91)	NR	High
	Placebo						264	-0.53 (10.52)		
	Natalizumab IV300					PCS	536	0.67 (8.05)		
	Placebo						264	-1.34 (8.47)		
OPERA I[67]	Ocrelizumab IV600	24M	NR			PCS	410	MD change from baseline=0.69 (95% CI -0.41, 1.80); p=0.22	NR	Low
	Interferon beta 1a SC44	24M					411			
OPERA II[67]	Ocrelizumab IV600	24M	NR			PCS	417	MD change from baseline=1.16 (95% CI 0.05, 2.27); p=0.04	NR	Low
	Interferon beta 1a SC44	24M					418			

Table 58 Quality of Life data (HARRMS population)

Study Name	Intervention	Timepoint	EQ-5D			SF-36			Other QoL measures reported	ROB
			N	Mean utility score (SD)	Mean VAS (SD)	Component	N	mean (SD or 95% CI)		
CARE-MS II[71]	Alemtuzumab IV12	24	412	No difference between groups (p>0.05)	Significantly greater improvement with Alemtuzumab	MCS	410	No difference between groups (p>0.05)	FAMS	High
	Interferon beta 1a SC44		173			PCS	172	Significantly greater improvement with Alemtuzumab (p<0.01)		
MIST[72]	AHCT	12	NR			Overall	49	70 (21.3)	NR	High
	iDMT						49	46.1 (22.5); p<0.001		

Appendix 5
Additional NMA Results

ARR (RRMS population)

Table 59 Comparison of results from fixed and random effects NMA for ARR (RRMS population)

	Fixed Effects	Random effects
Intervention	**RR (95% Credible interval)**	**RR (95% Credible interval)**
Alemtuzumab IV12	0.26 (0.19, 0.36)	0.26 (0.19, 0.36)
Cladribine O3.5	0.43 (0.34, 0.53)	0.42 (0.33, 0.54)
Fingolimod O0.5	0.45 (0.39, 0.52)	0.45 (0.39, 0.53)
Glatiramer acetate SC20	0.67 (0.60, 0.75)	0.67 (0.59, 0.77)
Glatiramer acetate SC40	0.69 (0.58, 0.83)	0.70 (0.57, 0.85)
Interferon beta 1a IM30	0.83 (0.73, 0.95)	0.84 (0.72, 0.97)
Interferon beta 1a SC22	0.69 (0.56, 0.84)	0.69 (0.55, 0.86)
Interferon beta 1a SC44	0.64 (0.56, 0.73)	0.64 (0.55, 0.74)
Interferon beta 1b IM 250	0.69 (0.60, 0.80)	0.70 (0.59, 0.82)
Natalizumab biosimilar	0.47 (0.23, 0.92)	0.47 (0.24, 0.99)
Natalizumab IV300	0.31 (0.24, 0.39)	0.31 (0.23, 0.40)
Ocrelizumab IV600	0.34 (0.27, 0.43)	0.34 (0.26, 0.44)
Ofatumumab SC20	0.49 (0.27, 0.86)	0.50 (0.28, 0.90)
Peginterferon beta 1a SC125	0.63 (0.49, 0.79)	0.62 (0.48, 0.81)
Ponesimod O20	0.76 (0.46, 1.28)	0.76 (0.45, 1.30)
Teriflunomide O14	1.08 (0.62, 1.89)	1.10 (0.63, 1.92)
Tau (95% CrI)	NA	0.05 (0.002, 0.14)
Mean log odds ratio	-0.59	-0.59
Residual deviance:	49.8 (on 55 data points)	49.9 (on 55 data points)
pD	27.9	30
DIC	77.7	79.9

Note: the random effects model had good convergence (all Rhat <1.01) and so informative priors were not needed.

Chosen model: Fixed effects model

Figure 28 Model fit for ARR assessed by individual study residual deviance (fixed effects analysis; RRMS population)

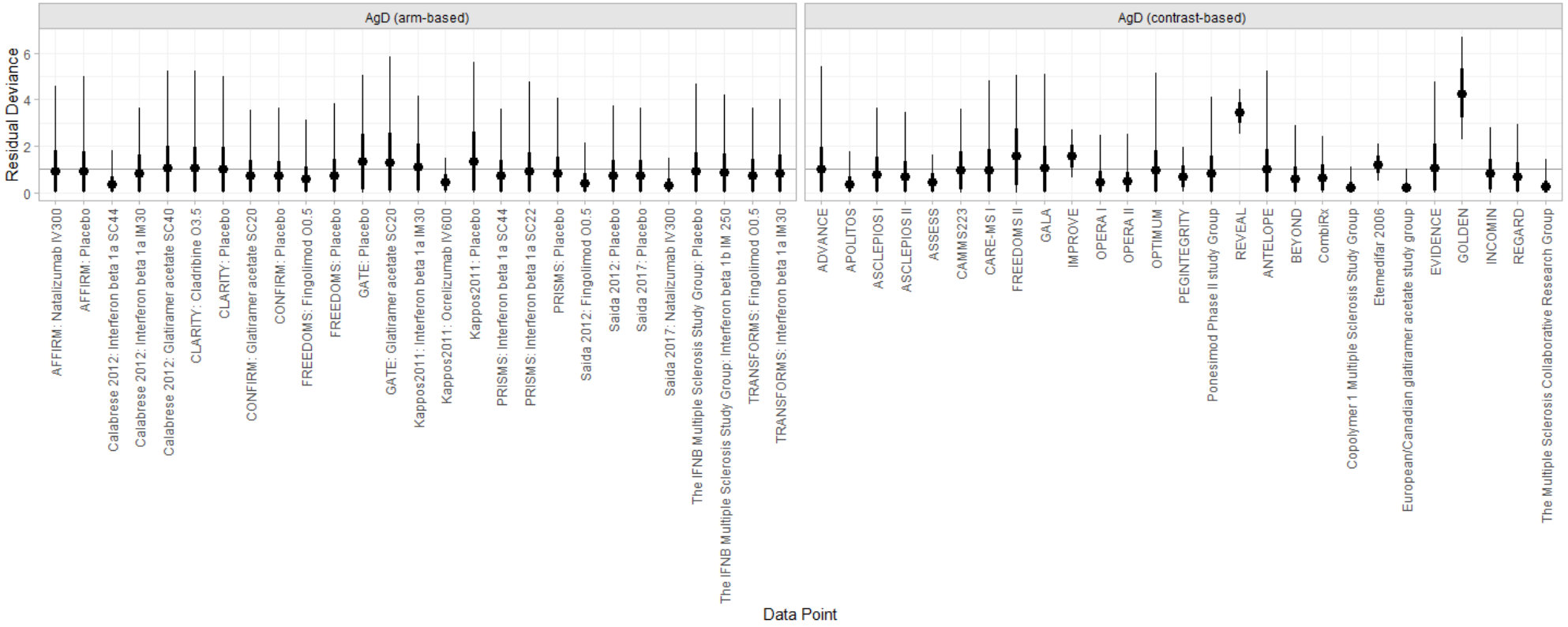

Table 60 Comparison (RR and 95% CrI) for each intervention pair for ARR (fixed effects analysis; RRMS population)

	Placebo	Alemtuzumab IV12	Cladribine O3.5	Fingolimod O0.5	Glatiramer acetate SC20	Glatiramer acetate SC40	Interferon beta 1a IM30	Interferon beta 1a SC22	Interferon beta 1a SC44	Interferon beta 1b IM 250	Natalizumab biosimilar	Natalizumab IV300	Ocrelizumab IV600	Ofatumumab SC20	Peginterferon beta 1a SC125	Ponesimod O20
Alemtuzumab IV12	0.26 (0.19, 0.36)															
Cladribine O3.5	0.43 (0.34, 0.53)	1.62 (1.10, 2.36)														
Fingolimod O0.5	0.45 (0.39, 0.52)	1.72 (1.22, 2.38)	1.06 (0.81, 1.39)													
Glatiramer acetate SC20	0.67 (0.60, 0.75)	2.56 (1.85, 3.51)	1.58 (1.22, 2.05)	1.49 (1.26, 1.77)												
Glatiramer acetate SC40	0.69 (0.58, 0.83)	2.63 (1.84, 3.73)	1.63 (1.23, 2.17)	1.53 (1.22, 1.93)	1.03 (0.83, 1.27)											
Interferon beta 1a IM30	0.83 (0.73, 0.95)	3.17 (2.30, 4.31)	1.96 (1.51, 2.54)	1.84 (1.55, 2.21)	1.24 (1.07, 1.45)	1.20 (0.98, 1.48)										
Interferon beta 1a SC22	0.69 (0.56, 0.84)	2.62 (1.84, 3.71)	1.62 (1.20, 2.20)	1.52 (1.20, 1.95)	1.02 (0.83, 1.28)	0.99 (0.76, 1.31)	0.83 (0.66, 1.03)									
Interferon beta 1a SC44	0.64 (0.56, 0.73)	2.44 (1.84, 3.20)	1.51 (1.16, 1.97)	1.42 (1.18, 1.72)	0.95 (0.82, 1.11)	0.93 (0.76, 1.14)	0.77 (0.67, 0.89)	0.93 (0.76, 1.14)								
Interferon beta 1b IM 250	0.69 (0.60, 0.80)	2.63 (1.88, 3.65)	1.62 (1.24, 2.11)	1.53 (1.27, 1.87)	1.03 (0.90, 1.19)	1.00 (0.80, 1.26)	0.83 (0.70, 0.98)	1.01 (0.79, 1.28)	1.08 (0.91, 1.29)							
Natalizumab biosimilar	0.47 (0.23, 0.92)	1.80 (0.82, 3.81)	1.11 (0.53, 2.29)	1.05 (0.50, 2.07)	0.70 (0.34, 1.40)	0.68 (0.33, 1.38)	0.57 (0.28, 1.13)	0.69 (0.33, 1.40)	0.74 (0.36, 1.46)	0.68 (0.33, 1.36)						
Natalizumab IV300	0.31 (0.24, 0.39)	1.16 (0.78, 1.70)	0.72 (0.51, 1.00)	0.68 (0.51, 0.90)	0.46 (0.35, 0.60)	0.44 (0.33, 0.59)	0.37 (0.27, 0.48)	0.45 (0.32, 0.61)	0.48 (0.36, 0.63)	0.44 (0.33, 0.58)	0.65 (0.34, 1.26)					
Ocrelizumab IV600	0.34 (0.27, 0.43)	1.29 (0.91, 1.81)	0.79 (0.57, 1.10)	0.75 (0.57, 0.99)	0.50 (0.39, 0.65)	0.49 (0.37, 0.65)	0.41 (0.32, 0.52)	0.49 (0.37, 0.66)	0.53 (0.43, 0.64)	0.49 (0.37, 0.64)	0.71 (0.35, 1.50)	1.10 (0.79, 1.53)				
Ofatumumab SC20	0.49 (0.27, 0.86)	1.87 (0.99, 3.65)	1.16 (0.63, 2.15)	1.09 (0.60, 1.93)	0.73 (0.40, 1.31)	0.71 (0.39, 1.30)	0.59 (0.33, 1.06)	0.72 (0.39, 1.31)	0.77 (0.43, 1.38)	0.71 (0.39, 1.28)	1.04 (0.43, 2.61)	1.61 (0.86, 3.01)	1.46 (0.79, 2.71)			
Peginterferon beta 1a SC125	0.63 (0.49, 0.79)	2.38 (1.63, 3.55)	1.47 (1.05, 2.05)	1.38 (1.05, 1.82)	0.93 (0.72, 1.21)	0.90 (0.67, 1.22)	0.75 (0.58, 0.98)	0.91 (0.67, 1.23)	0.98 (0.75, 1.29)	0.90 (0.69, 1.18)	1.32 (0.65, 2.82)	2.04 (1.45, 2.87)	1.85 (1.32, 2.59)	1.27 (0.70, 2.39)		
Ponesimod O20	0.76 (0.46, 1.28)	2.88 (1.60, 5.40)	1.78 (1.02, 3.18)	1.67 (0.98, 2.90)	1.13 (0.67, 1.96)	1.09 (0.64, 1.92)	0.91 (0.54, 1.57)	1.10 (0.64, 1.96)	1.18 (0.70, 2.03)	1.09 (0.64, 1.91)	1.60 (0.69, 3.85)	2.47 (1.42, 4.42)	2.24 (1.28, 4.02)	1.54 (1.10, 2.13)	1.21 (0.68, 2.15)	
Teriflunomide O14	1.08 (0.62, 1.89)	4.13 (2.25, 7.88)	2.55 (1.41, 4.69)	2.40 (1.35, 4.28)	1.61 (0.92, 2.83)	1.57 (0.89, 2.78)	1.30 (0.74, 2.31)	1.58 (0.88, 2.87)	1.69 (0.96, 2.95)	1.57 (0.87, 2.79)	2.29 (0.97, 5.60)	3.54 (1.94, 6.54)	3.21 (1.78, 5.91)	2.21 (1.79, 2.71)	1.73 (0.94, 3.16)	1.44 (1.11, 1.85)

Table 61 Probability that each intervention will rank in each position for ARR (fixed effects analysis; RRMS population)

	Probability of ranking position																
Intervention	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**
Placebo	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.01	0.16	0.61	1.00
Alemtuzumab IV12	0.72	0.91	0.98	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Cladribine O3.5	0.00	0.01	0.06	0.37	0.70	0.91	0.99	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Fingolimod O0.5	0.00	0.00	0.01	0.14	0.50	0.84	0.99	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Glatiramer acetate SC20	0.00	0.00	0.00	0.00	0.00	0.00	0.02	0.11	0.26	0.45	0.68	0.85	0.96	0.99	1.00	1.00	1.00
Glatiramer acetate SC40	0.00	0.00	0.00	0.00	0.00	0.00	0.04	0.12	0.22	0.36	0.49	0.65	0.84	0.96	0.99	1.00	1.00
Interferon beta 1a IM30	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.02	0.11	0.43	0.84	1.00	1.00
Interferon beta 1a SC22	0.00	0.00	0.00	0.00	0.00	0.01	0.05	0.13	0.25	0.38	0.52	0.67	0.83	0.95	0.99	1.00	1.00
Interferon beta 1a SC44	0.00	0.00	0.00	0.00	0.00	0.02	0.11	0.31	0.55	0.75	0.89	0.96	0.99	1.00	1.00	1.00	1.00
Interferon beta 1b IM 250	0.00	0.00	0.00	0.00	0.00	0.00	0.02	0.07	0.16	0.30	0.48	0.70	0.88	0.97	1.00	1.00	1.00
Natalizumab biosimilar	0.05	0.10	0.18	0.32	0.43	0.58	0.72	0.77	0.81	0.84	0.86	0.89	0.92	0.95	0.98	0.99	1.00
Natalizumab IV300	0.17	0.65	0.93	0.99	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Ocrelizumab IV600	0.04	0.27	0.71	0.93	0.99	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Ofatumumab SC20	0.02	0.06	0.12	0.24	0.36	0.55	0.75	0.80	0.84	0.87	0.89	0.92	0.97	0.99	1.00	1.00	1.00
Peginterferon beta 1a SC125	0.00	0.00	0.00	0.00	0.01	0.06	0.24	0.48	0.62	0.71	0.79	0.87	0.94	0.98	1.00	1.00	1.00
Ponesimod O20	0.00	0.00	0.00	0.00	0.01	0.03	0.09	0.21	0.27	0.32	0.36	0.42	0.50	0.65	0.85	1.00	1.00
Teriflunomide O14	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.01	0.02	0.03	0.04	0.05	0.07	0.11	0.19	0.40	1.00

ARR (RRMS population) – sensitivity analysis restricted to studies judged at low risk of bias

Figure 29 Network plot for NMA for ARR – studies at low risk of bias

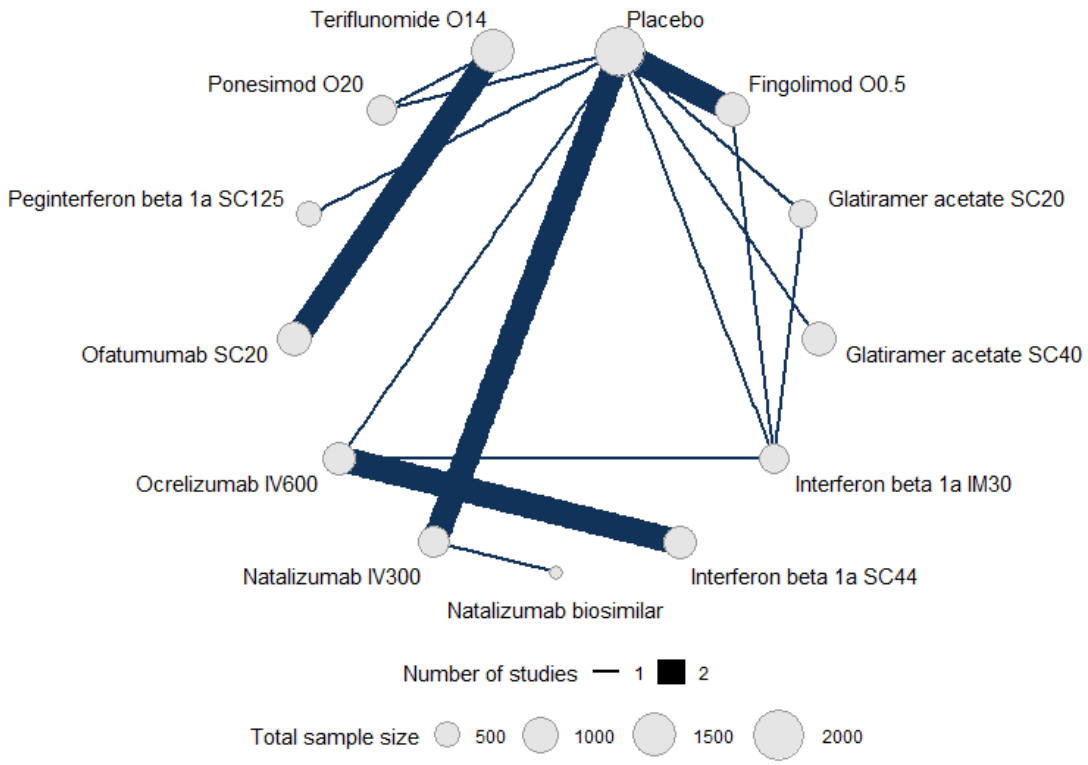

Table 62 Comparison of results from fixed and random effects NMA for ARR (RRMS population) – studies at low risk of bias

	Fixed Effects	Random effects
Intervention	**RR (95% Credible interval)**	**RR (95% Credible interval)**
Fingolimod O0.5	0.45 (0.36, 0.55)	0.45 (0.32, 0.60)
Glatiramer acetate SC20	0.70 (0.47, 1.05)	0.71 (0.45, 1.17)
Glatiramer acetate SC40	0.66 (0.54, 0.80)	0.65 (0.46, 0.95)
Interferon beta 1a IM30	0.89 (0.64, 1.23)	0.88 (0.57, 1.31)
Interferon beta 1a SC44	0.44 (0.13, 1.46)	0.45 (0.13, 1.61)
Natalizumab biosimilar	0.49 (0.25, 0.99)	0.48 (0.22, 1.09)
Natalizumab IV300	0.31 (0.25, 0.40)	0.31 (0.22, 0.45)
Ocrelizumab IV600	0.24 (0.07, 0.77)	0.24 (0.07, 0.81)
Ofatumumab SC20	0.52 (0.26, 1.01)	0.53 (0.23, 1.20)
Peginterferon beta 1a SC125	0.64 (0.50, 0.82)	0.64 (0.42, 0.92)
Ponesimod O20	0.79 (0.43, 1.41)	0.80 (0.41, 1.56)
Teriflunomide O14	1.14 (0.59, 2.15)	1.16 (0.55, 2.54)
Tau (95%CrI)	NA	0.12 (0.004, 0.40)
Mean log odds ratio	-0.58	-0.58
Residual deviance:	23.3 (on 25 data points)	23.4 (on 25 data points)
pD	19	20.4
DIC	42.2	43.9

Note: (all Rhat <1.01)

Parameters for the random effects model:

seed	437219664
prior_intercept	normal(0, scale = 5)
prior_trt	normal(0, scale = 10)
prior_het	half_normal(scale = 2)
adapt_delta	0.99

Table 63 Comparison of results from fixed and random effects NMA for ARR (RRMS population) – studies at low risk of bias

	p_rank[1]	p_rank[2]	p_rank[3]	p_rank[4]	p_rank[5]	p_rank[6]	p_rank[7]	p_rank[8]	p_rank[9]	p_rank[10]	p_rank[11]	p_rank[12]	p_rank[13]
Placebo	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.03	0.12	0.39	0.77	1.00
Fingolimod O0.5	0.00	0.06	0.27	0.61	0.89	0.98	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Glatiramer acetate SC20	0.00	0.00	0.01	0.03	0.10	0.22	0.37	0.54	0.75	0.89	0.97	0.99	1.00
Glatiramer acetate SC40	0.00	0.00	0.00	0.02	0.09	0.27	0.50	0.73	0.90	0.97	1.00	1.00	1.00
Interferon beta 1a IM30	0.00	0.00	0.00	0.00	0.00	0.01	0.02	0.07	0.21	0.45	0.71	0.91	1.00
Interferon beta 1a SC44	0.00	0.27	0.41	0.52	0.63	0.70	0.75	0.79	0.83	0.88	0.91	0.95	1.00
Natalizumab biosimilar	0.04	0.13	0.28	0.46	0.61	0.72	0.80	0.86	0.90	0.95	0.97	0.99	1.00
Natalizumab IV300	0.27	0.64	0.93	0.99	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Ocrelizumab IV600	0.66	0.79	0.87	0.91	0.94	0.96	0.97	0.98	0.99	0.99	1.00	1.00	1.00
Ofatumumab SC20	0.03	0.10	0.23	0.39	0.55	0.69	0.78	0.86	0.93	0.98	1.00	1.00	1.00
Peginterferon beta 1a SC125	0.00	0.00	0.01	0.04	0.13	0.32	0.56	0.76	0.89	0.97	1.00	1.00	1.00
Ponesimod O20	0.00	0.00	0.01	0.02	0.06	0.14	0.25	0.35	0.49	0.66	0.81	1.00	1.00
Teriflunomide O14	0.00	0.00	0.00	0.00	0.00	0.01	0.02	0.05	0.08	0.15	0.26	0.40	1.00

Disease progression: CDP3 (RRMS population)

Table 64 Comparison of results from fixed and random effects NMA for CDP3 (RRMS population)

	Fixed Effects	Random Effects
Intervention	**HR (95% Credible interval)**	**HR (95% Credible interval)**
Alemtuzumab IV12	0.26 (0.13, 0.53)	0.26 (0.11, 0.62)
Cladribine O3.5	0.67 (0.48, 0.95)	0.67 (0.42, 1.04)
Fingolimod O0.5	0.77 (0.63, 0.94)	0.77 (0.55, 1.05)
Glatiramer acetate SC20	0.91 (0.66, 1.24)	0.91 (0.60, 1.34)
Interferon beta 1a IM30	0.72 (0.49, 1.06)	0.73 (0.43, 1.21)
Interferon beta 1a SC22	0.55 (0.35, 0.85)	0.55 (0.31, 0.98)
Interferon beta 1a SC44	0.62 (0.43, 0.89)	0.63 (0.38, 1.02)
Interferon beta 1b IM 250	1.21 (0.82, 1.78)	1.20 (0.66, 2.16)
Natalizumab IV300	0.58 (0.43, 0.76)	0.58 (0.37, 0.93)
Ocrelizumab IV600	0.38 (0.24, 0.61)	0.38 (0.19, 0.70)
Peginterferon beta 1a SC125	0.61 (0.39, 0.95)	0.61 (0.33, 1.07)
Tau (95% CrI)	NA	0.14 (0.005, 0.5)
Mean log odds	-0.48	-0.48
Residual deviance	11.8 (on 16 data points)	12.8 (on 16 data points)
pD	11	12.3
DIC	22.8	25.1

Note: (all Rhat <1.01)

Parameters for the random effects model:

prior_intercept	normal(0, scale = 10)
prior_trt	normal(0, scale = 10)
prior_het	half_normal(scale = 2)
adapt_delta	0.999

Chosen model: Fixed effects model

Figure 30 Model fit for CDP3 assessed by individual study residual deviance (fixed effects analysis; RRMS population)

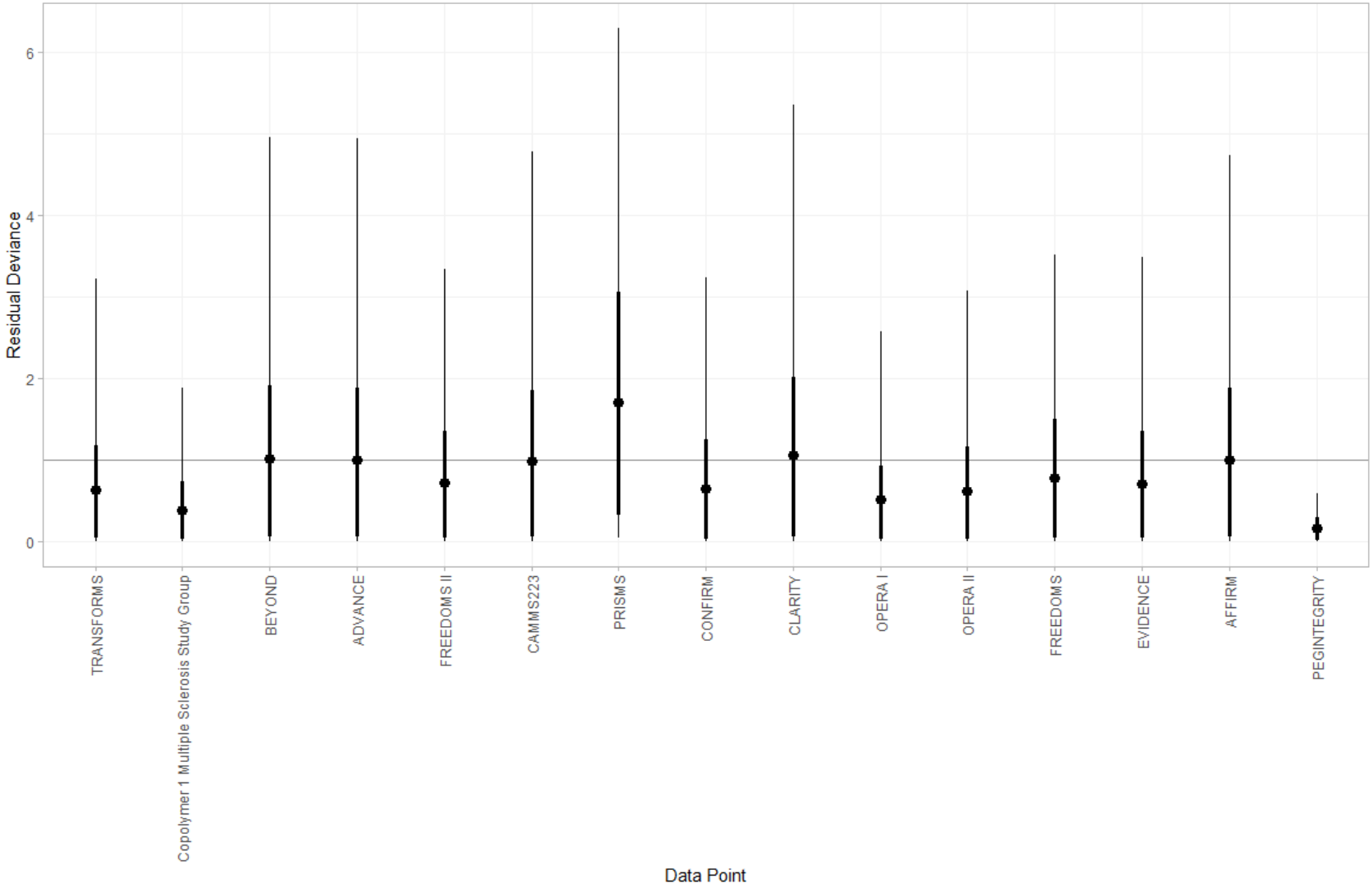

Table 65 Comparison (HR and 95% CrI) for each intervention pair for CDP3 (random effects analysis; RRMS population)

	Placebo	Alemtuzumab IV12	Cladribine O3.5	Fingolimod O0.5	Glatiramer acetate SC20	Interferon beta 1a IM30	Interferon beta 1a SC22	Interferon beta 1a SC44	Interferon beta 1b IM 250	Natalizumab IV300	Ocrelizumab IV600
Alemtuzumab IV12	0.26 (0.13, 0.53)										
Cladribine O3.5	0.67 (0.48, 0.95)	2.57 (1.19, 5.60)									
Fingolimod O0.5	0.77 (0.63, 0.94)	2.92 (1.43, 5.87)	1.14 (0.76, 1.70)								
Glatiramer acetate SC20	0.91 (0.66, 1.24)	3.48 (1.62, 7.35)	1.35 (0.85, 2.11)	1.19 (0.81, 1.72)							
Interferon beta 1a IM30	0.72 (0.49, 1.06)	2.75 (1.39, 5.44)	1.07 (0.63, 1.80)	0.94 (0.65, 1.38)	0.79 (0.49, 1.31)						
Interferon beta 1a SC22	0.55 (0.35, 0.85)	2.10 (0.92, 4.73)	0.82 (0.47, 1.42)	0.72 (0.44, 1.15)	0.60 (0.35, 1.02)	0.76 (0.42, 1.40)					
Interferon beta 1a SC44	0.62 (0.43, 0.89)	2.38 (1.31, 4.26)	0.93 (0.57, 1.53)	0.81 (0.56, 1.17)	0.68 (0.43, 1.09)	0.87 (0.62, 1.22)	1.14 (0.64, 2.02)				
Interferon beta 1b IM 250	1.21 (0.82, 1.78)	4.60 (2.05, 10.32)	1.79 (1.06, 2.99)	1.57 (1.01, 2.41)	1.32 (1.04, 1.68)	1.67 (0.95, 2.92)	2.20 (1.22, 4.00)	1.93 (1.13, 3.28)			
Natalizumab IV300	0.58 (0.43, 0.76)	2.21 (1.05, 4.76)	0.86 (0.55, 1.33)	0.76 (0.54, 1.08)	0.64 (0.42, 0.98)	0.80 (0.50, 1.31)	1.06 (0.62, 1.78)	0.93 (0.59, 1.48)	0.48 (0.30, 0.79)		
Ocrelizumab IV600	0.38 (0.24, 0.61)	1.44 (0.74, 2.81)	0.56 (0.32, 1.01)	0.49 (0.30, 0.80)	0.41 (0.24, 0.73)	0.52 (0.33, 0.81)	0.68 (0.36, 1.30)	0.60 (0.45, 0.81)	0.31 (0.17, 0.57)	0.65 (0.38, 1.13)	
Peginterferon beta 1a SC125	0.61 (0.39, 0.95)	2.34 (1.04, 5.26)	0.91 (0.53, 1.57)	0.80 (0.49, 1.30)	0.67 (0.40, 1.13)	0.85 (0.47, 1.50)	1.11 (0.60, 2.09)	0.98 (0.56, 1.69)	0.51 (0.28, 0.91)	1.06 (0.63, 1.77)	1.63 (0.84, 3.04)

Table 66 Probability that each intervention will rank in each position for CDP3 (random effects analysis; RRMS population)

	p_rank[1]	p_rank[2]	p_rank[3]	p_rank[4]	p_rank[5]	p_rank[6]	p_rank[7]	p_rank[8]	p_rank[9]	p_rank[10]	p_rank[11]	p_rank[12]
Placebo	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.02	0.32	0.84	1.00
Alemtuzumab IV12	0.83	0.96	0.98	0.99	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Cladribine O3.5	0.00	0.01	0.07	0.18	0.33	0.50	0.67	0.81	0.94	0.98	1.00	1.00
Fingolimod O0.5	0.00	0.00	0.00	0.01	0.04	0.11	0.28	0.58	0.90	0.99	1.00	1.00
Glatiramer acetate SC20	0.00	0.00	0.00	0.00	0.01	0.04	0.08	0.16	0.33	0.73	1.00	1.00
Interferon beta 1a IM30	0.00	0.00	0.03	0.09	0.19	0.33	0.50	0.70	0.86	0.95	0.98	1.00
Interferon beta 1a SC22	0.02	0.12	0.40	0.58	0.72	0.82	0.89	0.95	0.99	1.00	1.00	1.00
Interferon beta 1a SC44	0.00	0.00	0.12	0.30	0.50	0.69	0.85	0.94	0.98	1.00	1.00	1.00
Interferon beta 1b IM 250	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.01	0.02	0.06	0.19	1.00
Natalizumab IV300	0.00	0.04	0.24	0.48	0.69	0.84	0.93	0.97	1.00	1.00	1.00	1.00
Ocrelizumab IV600	0.14	0.82	0.94	0.98	0.99	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Peginterferon beta 1a SC125	0.01	0.05	0.21	0.38	0.53	0.67	0.79	0.88	0.95	0.99	1.00	1.00

Disease progression: CDP6 (RRMS population)

Table 67 Comparison of results from fixed and random effects NMA for CDP6 (RRMS population)

Note: the random effects model had good convergence and so informative priors were not needed.

	Fixed effects	Random Effects
Intervention	**HR (95% Credible interval)**	**HR (95% Credible interval)**
Alemtuzumab IV12	0.34 (0.14, 0.80)	0.29 (0.05, 1.42)
Cladribine O3.5	0.98 (0.79, 1.20)	0.99 (0.33, 2.94)
Fingolimod O0.5	0.67 (0.51, 0.88)	0.67 (0.31, 1.44)
Glatiramer acetate SC20	0.63 (0.31, 1.25)	0.60 (0.16, 2.65)
Interferon beta 1a IM30	0.64 (0.35, 1.16)	0.65 (0.21, 2.05)
Interferon beta 1a SC44	0.67 (0.32, 1.39)	0.63 (0.15, 2.52)
Interferon beta 1b IM 250	0.28 (0.12, 0.66)	0.29 (0.06, 1.47)
Natalizumab IV300	0.46 (0.33, 0.63)	0.46 (0.17, 1.28)
Ocrelizumab IV600	0.40 (0.18, 0.91)	0.38 (0.07, 1.95)
Peginterferon beta 1a SC125	0.46 (0.26, 0.81)	0.47 (0.15, 1.50)
Tau (95% CrI)	NA	0.39 (0.02, 1.19)
Mean log odds	-0.65	-0.68
Residual deviance	17.9 (on 14 data points)	14.9 on 14 data points
pD	10	12.9
DIC	28	27.9

(all Rhat <1.01)

Parameters for the random effects model:

Seed	437219664
trt_effects	"random"
prior_intercept	normal(0, scale = 10)
prior_trt	normal(0, scale = 10)
prior_het	half_normal(scale = 2)
control	list(max_treedepth = 12),
adapt_delta	0.999

Chosen model: Fixed effects model

Figure 31 Model fit for CDP6 assessed by individual study residual deviance (random effects analysis; RRMS population)

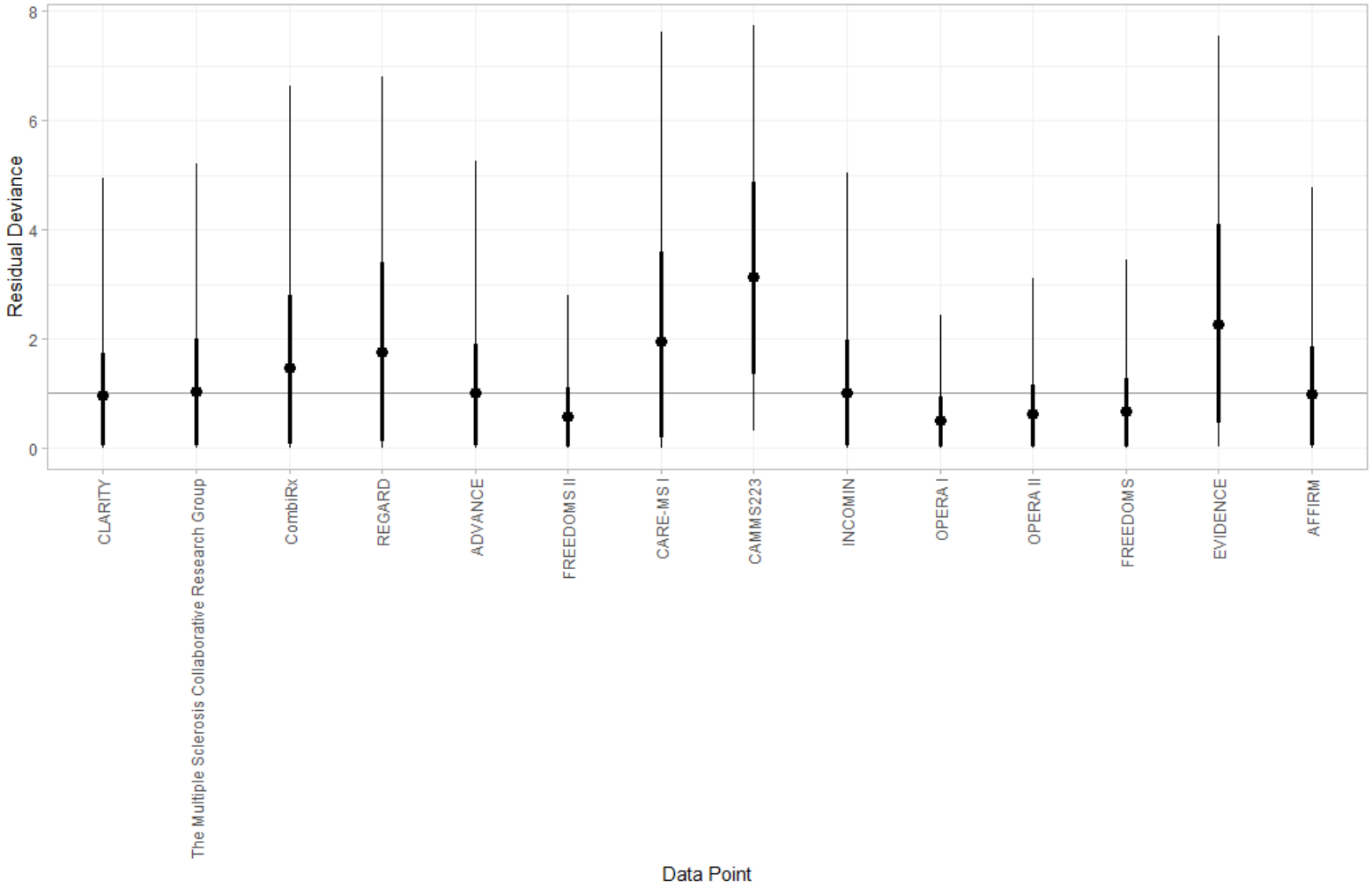

Table 68 Comparison (HR and 95% CrI) for each intervention pair for CDP6 (fixed effects analysis; RRMS population)

	Placebo	Alemtuzumab IV12	Cladribine O3.5	Fingolimod O0.5	Glatiramer acetate SC20	Interferon beta 1a IM30	Interferon beta 1a SC44	Interferon beta 1b IM 250	Natalizumab IV300	Ocrelizumab IV600
Alemtuzumab IV12	0.34 (0.14, 0.80)									
Cladribine O3.5	0.98 (0.79, 1.20)	2.88 (1.18, 7.20)								
Fingolimod O0.5	0.67 (0.51, 0.88)	1.98 (0.79, 4.90)	0.69 (0.49, 0.96)							
Glatiramer acetate SC20	0.63 (0.31, 1.25)	1.88 (1.05, 3.40)	0.65 (0.32, 1.34)	0.95 (0.45, 1.93)						
Interferon beta 1a IM30	0.64 (0.35, 1.16)	1.90 (1.02, 3.54)	0.66 (0.35, 1.23)	0.96 (0.50, 1.83)	1.01 (0.73, 1.41)					
Interferon beta 1a SC44	0.67 (0.32, 1.39)	1.98 (1.24, 3.15)	0.69 (0.31, 1.49)	1.00 (0.46, 2.16)	1.05 (0.73, 1.53)	1.04 (0.69, 1.58)				
Interferon beta 1b IM 250	0.28 (0.12, 0.66)	0.84 (0.36, 1.93)	0.29 (0.12, 0.70)	0.42 (0.18, 1.03)	0.45 (0.23, 0.87)	0.44 (0.25, 0.78)	0.42 (0.21, 0.85)			
Natalizumab IV300	0.46 (0.33, 0.63)	1.36 (0.54, 3.47)	0.47 (0.32, 0.70)	0.69 (0.46, 1.03)	0.73 (0.34, 1.59)	0.72 (0.38, 1.44)	0.69 (0.31, 1.55)	1.62 (0.67, 4.00)		
Ocrelizumab IV600	0.40 (0.18, 0.91)	1.20 (0.67, 2.15)	0.41 (0.17, 0.95)	0.60 (0.26, 1.44)	0.64 (0.38, 1.06)	0.63 (0.36, 1.08)	0.60 (0.43, 0.85)	1.42 (0.64, 3.16)	0.88 (0.36, 2.09)	
Peginterferon beta 1a SC125	0.46 (0.26, 0.81)	1.35 (0.48, 3.79)	0.47 (0.26, 0.87)	0.68 (0.37, 1.30)	0.72 (0.30, 1.77)	0.71 (0.32, 1.60)	0.68 (0.27, 1.74)	1.61 (0.59, 4.42)	0.99 (0.51, 1.89)	1.13 (0.43, 2.96)

Table 69 Probability that each intervention will rank in each position for CDP6 (fixed effects analysis; RRMS population)

	p_rank[1]	p_rank[2]	p_rank[3]	p_rank[4]	p_rank[5]	p_rank[6]	p_rank[7]	p_rank[8]	p_rank[9]	p_rank[10]	p_rank[11]
Placebo	0.00	0.00	0.01	0.02	0.04	0.07	0.11	0.19	0.31	0.68	1.00
Alemtuzumab IV12	0.30	0.57	0.73	0.83	0.90	0.93	0.96	0.97	0.99	1.00	1.00
Cladribine O3.5	0.01	0.02	0.04	0.07	0.10	0.15	0.20	0.27	0.39	0.63	1.00
Fingolimod O0.5	0.01	0.04	0.09	0.17	0.27	0.39	0.50	0.64	0.89	0.96	1.00
Glatiramer acetate SC20	0.01	0.03	0.08	0.19	0.33	0.48	0.64	0.76	0.87	0.93	1.00
Interferon beta 1a IM30	0.00	0.01	0.03	0.08	0.18	0.37	0.58	0.76	0.89	0.96	1.00
Interferon beta 1a SC44	0.00	0.01	0.04	0.14	0.27	0.42	0.57	0.71	0.83	0.91	1.00
Interferon beta 1b IM 250	0.38	0.58	0.73	0.82	0.88	0.92	0.95	0.97	0.98	0.99	1.00
Natalizumab IV300	0.09	0.22	0.36	0.50	0.63	0.72	0.81	0.90	0.95	0.98	1.00
Ocrelizumab IV600	0.10	0.30	0.53	0.69	0.80	0.87	0.91	0.95	0.97	0.99	1.00
Peginterferon beta 1a SC125	0.11	0.23	0.36	0.50	0.60	0.69	0.77	0.87	0.94	0.97	1.00

Disease progression: CDP3 and CDP6 combined (RRMS population)

Table 70 Comparison of results from fixed and random effects NMA for CDP3 and CDP6 combined (RRMS population)

	Fixed effects	Random Effects
Intervention	**HR (95% Credible interval)**	**HR (95% Credible interval)**
Alemtuzumab IV12	0.36 (0.21, 0.63)	0.33 (0.14, 0.77)
Cladribine O3.5	0.98 (0.78, 1.22)	0.97 (0.44, 2.04)
Fingolimod O0.5	0.71 (0.55, 0.90)	0.73 (0.45, 1.19)
Glatiramer acetate SC20	0.72 (0.57, 0.92)	0.71 (0.44, 1.12)
Interferon beta 1a IM30	0.80 (0.61, 1.05)	0.81 (0.49, 1.30)
Interferon beta 1a SC22	0.55 (0.36, 0.87)	0.57 (0.26, 1.34)
Interferon beta 1a SC44	0.71 (0.52, 0.96)	0.71 (0.40, 1.23)
Interferon beta 1b IM 250	0.83 (0.60, 1.15)	0.66 (0.29, 1.29)
Natalizumab IV300	0.46 (0.33, 0.64)	0.46 (0.21, 1.02)
Ocrelizumab IV600	0.43 (0.27, 0.68)	0.43 (0.19, 0.98)
Peginterferon beta 1a SC125	0.46 (0.27, 0.80	0.46 (0.19, 1.08)
Tau (95% CrI)	NA	0.33 (0.07, 0.69)
Mean log odds	-0.50	-0.52
Residual deviance	33.2 (on 21 data points)	21.3 (on 21 data points)
pD	11.1	117.3
DIC	44.3	38.7

Note: the random effects model had good convergence (all Rhat <1.01) and so informative priors were not needed.

Chosen model: Fixed effects model

Figure 32 Model fit for CDP3 and CDP6 combined assessed by individual study residual deviance (random effects analysis; RRMS population)

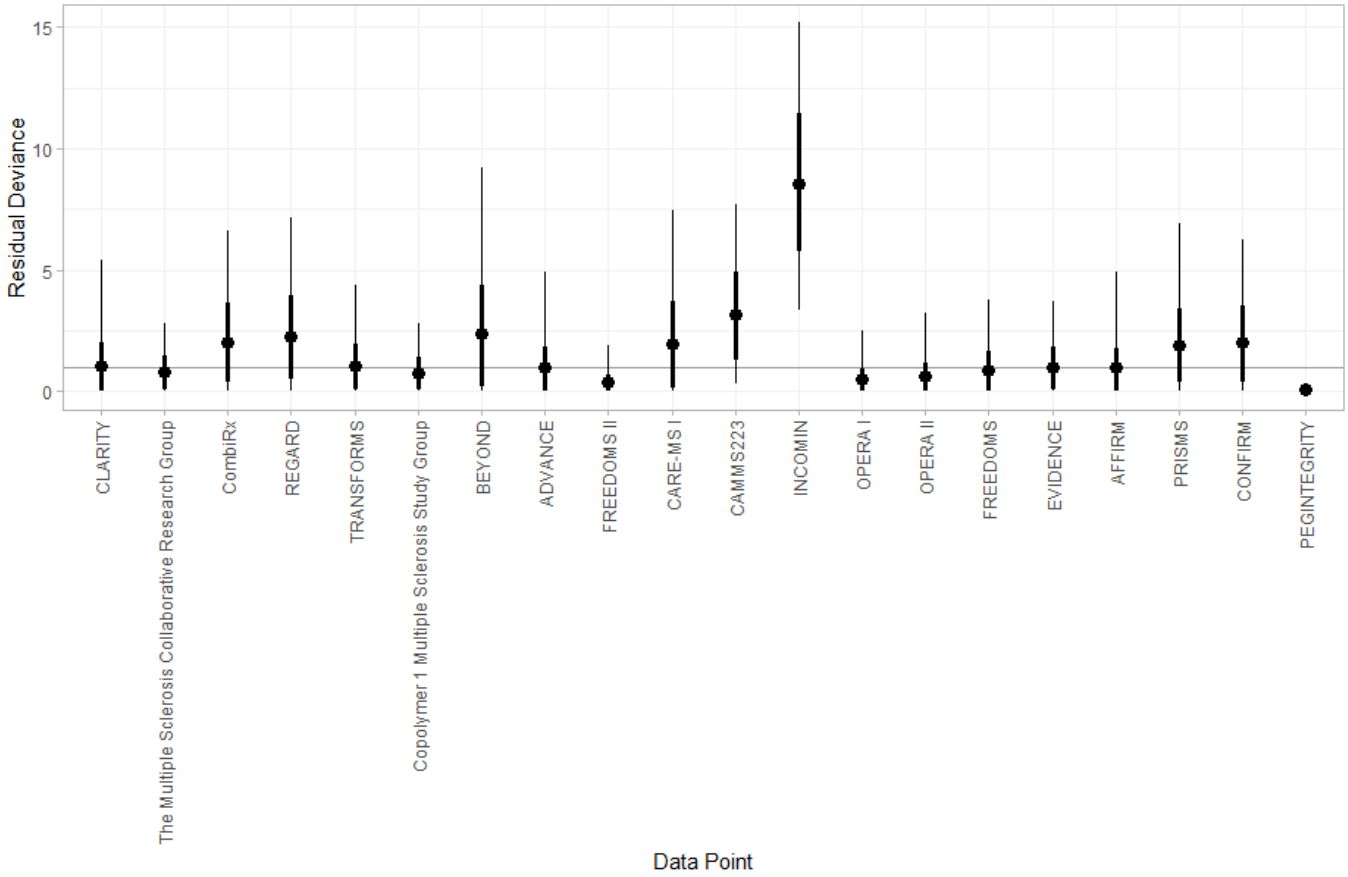

Table 71 Comparison (HR and 95% CrI) for each intervention pair for CDP3 and CDP6 combined (fixed effects analysis; RRMS population)

	Placebo	Alemtuzumab IV12	Cladribine O3.5	Fingolimod O0.5	Glatiramer acetate SC20	Interferon beta 1a IM30	Interferon beta 1a SC22	Interferon beta 1a SC44	Interferon beta 1b IM 250	Natalizumab IV300	Ocrelizumab IV600
Alemtuzumab IV12	0.36 (0.21, 0.63)										
Cladribine O3.5	0.98 (0.78, 1.22)	2.71 (1.49, 4.86)									
Fingolimod O0.5	0.71 (0.55, 0.90)	1.96 (1.09, 3.53)	0.72 (0.52, 1.00)								
Glatiramer acetate SC20	0.72 (0.57, 0.92)	2.01 (1.17, 3.50)	0.74 (0.53, 1.02)	1.02 (0.74, 1.41)							
Interferon beta 1a IM30	0.80 (0.61, 1.05)	2.22 (1.24, 3.87)	0.82 (0.58, 1.16)	1.13 (0.84, 1.55)	1.10 (0.85, 1.42)						
Interferon beta 1a SC22	0.55 (0.36, 0.87)	1.52 (0.74, 3.01)	0.56 (0.35, 0.92)	0.78 (0.47, 1.30)	0.76 (0.46, 1.28)	0.69 (0.41, 1.16)					
Interferon beta 1a SC44	0.71 (0.52, 0.96)	1.97 (1.25, 3.12)	0.73 (0.50, 1.07)	1.01 (0.70, 1.45)	0.98 (0.72, 1.33)	0.89 (0.65, 1.24)	1.30 (0.76, 2.21)				
Interferon beta 1b IM 250	0.83 (0.60, 1.15)	2.29 (1.27, 4.15)	0.85 (0.58, 1.24)	1.17 (0.81, 1.70)	1.14 (0.91, 1.43)	1.03 (0.76, 1.40)	1.51 (0.87, 2.57)	1.16 (0.81, 1.68)			
Natalizumab IV300	0.46 (0.33, 0.64)	1.28 (0.66, 2.44)	0.47 (0.32, 0.70)	0.65 (0.43, 0.98)	0.64 (0.42, 0.95)	0.58 (0.38, 0.88)	0.84 (0.48, 1.47)	0.65 (0.42, 1.03)	0.56 (0.35, 0.88)		
Ocrelizumab IV600	0.43 (0.27, 0.68)	1.19 (0.67, 2.08)	0.44 (0.26, 0.74)	0.61 (0.37, 1.00)	0.59 (0.38, 0.93)	0.54 (0.33, 0.86)	0.78 (0.42, 1.47)	0.60 (0.43, 0.85)	0.52 (0.32, 0.84)	0.93 (0.54, 1.62)	
Peginterferon beta 1a SC125	0.46 (0.27, 0.80)	1.29 (0.58, 2.82)	0.47 (0.26, 0.85)	0.66 (0.35, 1.19)	0.64 (0.35, 1.18)	0.58 (0.31, 1.10)	0.84 (0.42, 1.68)	0.65 (0.34, 1.23)	0.56 (0.30, 1.06)	1.01 (0.52, 1.93)	1.08 (0.53, 2.20)

Table 72 Probability that each intervention will rank in each position for CDP3 and CDP6 combined (fixed effects analysis; RRMS population)

	p_rank[1]	p_rank[2]	p_rank[3]	p_rank[4]	p_rank[5]	p_rank[6]	p_rank[7]	p_rank[8]	p_rank[9]	p_rank[10]	p_rank[11]	p_rank[12]
Placebo	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.01	0.09	0.51	1.00
Alemtuzumab IV12	0.53	0.74	0.87	0.95	0.99	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Cladribine O3.5	0.00	0.00	0.00	0.00	0.00	0.00	0.02	0.04	0.11	0.24	0.63	1.00
Fingolimod O0.5	0.00	0.00	0.00	0.04	0.16	0.42	0.62	0.78	0.90	0.99	1.00	1.00
Glatiramer acetate SC20	0.00	0.00	0.00	0.02	0.09	0.29	0.58	0.83	0.97	1.00	1.00	1.00
Interferon beta 1a IM30	0.00	0.00	0.00	0.00	0.02	0.08	0.20	0.39	0.66	0.91	0.97	1.00
Interferon beta 1a SC22	0.04	0.11	0.25	0.47	0.76	0.85	0.90	0.94	0.97	0.99	1.00	1.00
Interferon beta 1a SC44	0.00	0.00	0.00	0.03	0.15	0.39	0.61	0.76	0.89	0.97	0.99	1.00
Interferon beta 1b IM 250	0.00	0.00	0.00	0.01	0.02	0.07	0.15	0.29	0.51	0.82	0.91	1.00
Natalizumab IV300	0.10	0.32	0.59	0.85	0.97	0.99	0.99	1.00	1.00	1.00	1.00	1.00
Ocrelizumab IV600	0.16	0.47	0.73	0.88	0.98	0.99	1.00	1.00	1.00	1.00	1.00	1.00
Peginterferon beta 1a SC125	0.18	0.36	0.55	0.74	0.88	0.93	0.95	0.97	0.98	0.99	1.00	1.00

MRI Gd+ lesions (RRMS population)

Table 73 Comparison of results from fixed and random effects NMA for MRI Gd+ lesions (RRMS population)

	Fixed effects	Random Effects
Intervention	**HR (95% Credible interval)**	**HR (95% Credible interval)**
Alemtuzumab IV12	0.20 (0.11, 0.35)	0.19 (0.10, 0.37)
Cladribine O3.5	0.24 (0.18, 0.33)	0.24 (0.16, 0.37)
Fingolimod O0.5	0.33 (0.27, 0.40)	0.33 (0.26, 0.42)
Glatiramer acetate SC20	0.77 (0.62, 0.95)	0.76 (0.58, 0.99)
Interferon beta 1a IM30	0.60 (0.47, 0.75)	0.61 (0.46, 0.81)
Interferon beta 1a SC44	0.53 (0.42, 0.67)	0.52 (0.38, 0.69)
Interferon beta 1b IM 250	0.28 (0.15, 0.51)	0.28 (0.15, 0.56)
Natalizumab biosimilar	0.11 (0.05, 0.22)	0.11 (0.05, 0.25)
Natalizumab IV300	0.14 (0.09, 0.21)	0.14 (0.09, 0.22)
Ocrelizumab IV600	0.09 (0.06, 0.13	0.09 (0.05, 0.14)
Tau (95%CrI)	NA	0.11 (0.006, 0.32)
Mean log odds ratio	-1.35	-1.35
Residual deviance	17.8 (on 19 data points)	16.5 (on 19 data points)
pD	10.2	12
DIC	27.9	28.5

Note: the random effects model had good convergence (all Rhat <1.01) and so informative priors were not needed.

Chosen model: Fixed effects model

Figure 33 Model fit for MRI Gd+ lesions combined assessed by individual study residual deviance (fixed effects analysis; RRMS population)

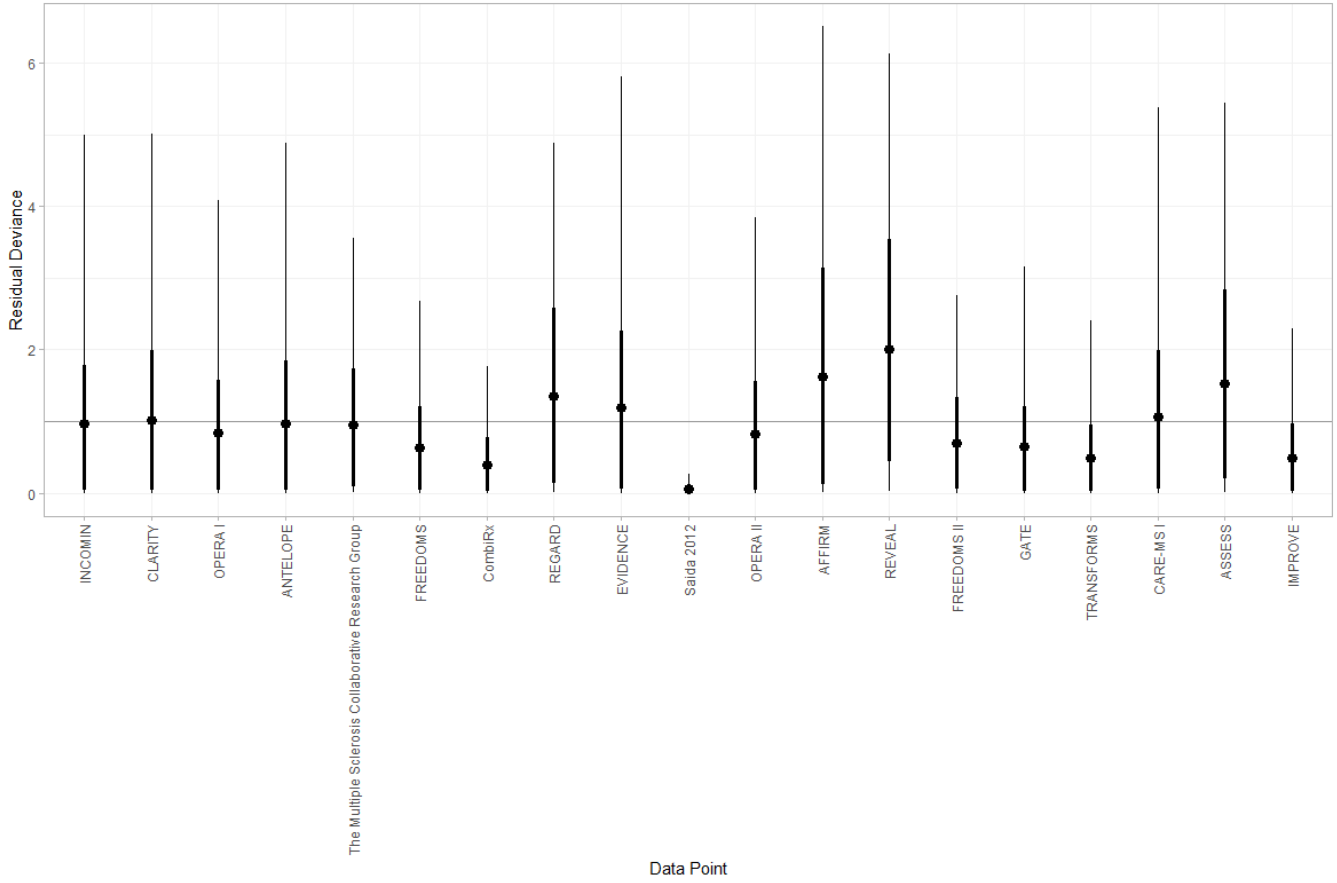

Table 74 Comparison (HR and 95% CrI) for each intervention pair for MRI Gd+ lesions (fixed effects analysis; RRMS population)

	Placebo	Alemtuzumab IV12	Cladribine O3.5	Fingolimod O0.5	Glatiramer acetate SC20	Interferon beta 1a IM30	Interferon beta 1a SC44	Interferon beta 1b IM 250	Natalizumab biosimilar	Natalizumab IV300
Alemtuzumab IV12	0.20 (0.11, 0.35)									
Cladribine O3.5	0.24 (0.18, 0.33)	1.23 (0.64, 2.39)								
Fingolimod O0.5	0.33 (0.27, 0.40)	1.66 (0.94, 2.99)	1.35 (0.94, 1.94)							
Glatiramer acetate SC20	0.77 (0.62, 0.95)	3.87 (2.16, 7.01)	3.14 (2.14, 4.56)	2.33 (1.83, 3.00)						
Interferon beta 1a IM30	0.60 (0.47, 0.75)	3.01 (1.76, 5.25)	2.45 (1.68, 3.60)	1.82 (1.42, 2.34)	0.78 (0.61, 0.99)					
Interferon beta 1a SC44	0.53 (0.42, 0.67)	2.69 (1.61, 4.66)	2.19 (1.51, 3.19)	1.62 (1.25, 2.11)	0.70 (0.55, 0.88)	0.89 (0.77, 1.04)				
Interferon beta 1b IM 250	0.28 (0.15, 0.51)	1.41 (0.65, 3.08)	1.15 (0.59, 2.20)	0.85 (0.47, 1.56)	0.36 (0.20, 0.67)	0.47 (0.27, 0.81)	0.52 (0.30, 0.93)			
Natalizumab biosimilar	0.11 (0.05, 0.22)	0.55 (0.22, 1.36)	0.44 (0.20, 0.98)	0.33 (0.16, 0.69)	0.14 (0.07, 0.30)	0.18 (0.09, 0.39)	0.20 (0.10, 0.43)	0.39 (0.15, 0.98)		
Natalizumab IV300	0.14 (0.09, 0.21)	0.70 (0.35, 1.44)	0.57 (0.35, 0.97)	0.42 (0.29, 0.64)	0.18 (0.12, 0.28)	0.23 (0.15, 0.36)	0.26 (0.17, 0.41)	0.50 (0.25, 1.00)	1.29 (0.69, 2.37)	
Ocrelizumab IV600	0.09 (0.06, 0.13)	0.44 (0.24, 0.83)	0.36 (0.22, 0.59)	0.27 (0.17, 0.41)	0.11 (0.08, 0.17)	0.15 (0.10, 0.21)	0.16 (0.12, 0.23)	0.31 (0.16, 0.62)	0.81 (0.35, 1.85)	0.63 (0.36, 1.10)

Table 75 Probability that each intervention will rank in each position for MRI Gd+ lesions (fixed effects analysis; RRMS population)

	p_rank[1]	p_rank[2]	p_rank[3]	p_rank[4]	p_rank[5]	p_rank[6]	p_rank[7]	p_rank[8]	p_rank[9]	p_rank[10]	p_rank[11]
Placebo	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.01	1.00
Alemtuzumab IV12	0.00	0.06	0.19	0.66	0.87	0.97	1.00	1.00	1.00	1.00	1.00
Cladribine O3.5	0.00	0.00	0.02	0.22	0.69	0.96	1.00	1.00	1.00	1.00	1.00
Fingolimod O0.5	0.00	0.00	0.00	0.00	0.04	0.36	1.00	1.00	1.00	1.00	1.00
Glatiramer acetate SC20	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.02	0.99	1.00
Interferon beta 1a IM30	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.08	0.98	1.00	1.00
Interferon beta 1a SC44	0.00	0.00	0.00	0.00	0.00	0.00	0.01	0.92	1.00	1.00	1.00
Interferon beta 1b IM 250	0.00	0.01	0.03	0.15	0.40	0.71	0.99	0.99	1.00	1.00	1.00
Natalizumab biosimilar	0.30	0.76	0.92	0.98	0.99	1.00	1.00	1.00	1.00	1.00	1.00
Natalizumab IV300	0.01	0.22	0.85	0.99	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Ocrelizumab IV600	0.68	0.95	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00

MRI T2 weighted lesions (RRMS population)

Table 76 Comparison of results from fixed and random effects NMA for MRI T2 weighted lesions (RRMS population)

	Fixed effects	Random Effects
Intervention	**HR (95% Credible interval)**	**HR (95% Credible interval)**
Alemtuzumab IV12	0.61 (0.45, 0.81)	0.60 (0.41, 0.86)
Cladribine O3.5	0.52 (0.43, 0.64)	0.52 (0.39, 0.69)
Fingolimod O0.5	0.63 (0.55, 0.72)	0.63 (0.53, 0.73)
Glatiramer acetate SC20	0.80 (0.66, 0.98)	0.79 (0.61, 1.01)
Interferon beta 1a IM30	0.77 (0.64, 0.92)	0.75 (0.59, 0.95)
Interferon beta 1a SC22	0.88 (0.71, 1.10)	0.87 (0.66, 1.15)
Interferon beta 1a SC44	0.72 (0.61, 0.85)	0.71 (0.57, 0.86)
Interferon beta 1b IM 250	0.46 (0.29, 0.73)	0.46 (0.27, 0.76)
Natalizumab biosimilar	0.46 (0.30, 0.70)	0.46 (0.28, 0.74)
Natalizumab IV300	0.50 (0.42, 0.59)	0.49 (0.38, 0.62)
Ocrelizumab IV600	0.44 (0.36, 0.55)	0.43 (0.32, 0.57)
Tau	NA	0.07 (0.002, 0.25)
Mean log odds ratio	-0.51	-0.52
Residual deviance	15.4 (on 18 data points)	15.6 (on 18 data points)
pD	11	12.3
DIC	26.4	27.9

(all Rhat <1.01)

RE parameters:

seed	437219664
prior_intercept	normal(0, scale = 10)
prior_trt	normal(0, scale = 10)
prior_het	half_normal(scale = 2)
adapt_delta	0.999

Chosen model: Fixed effects model

Figure 34 Model fit for MRI T2 weighted lesions assessed by individual study residual deviance (fixed effects analysis; RRMS population)

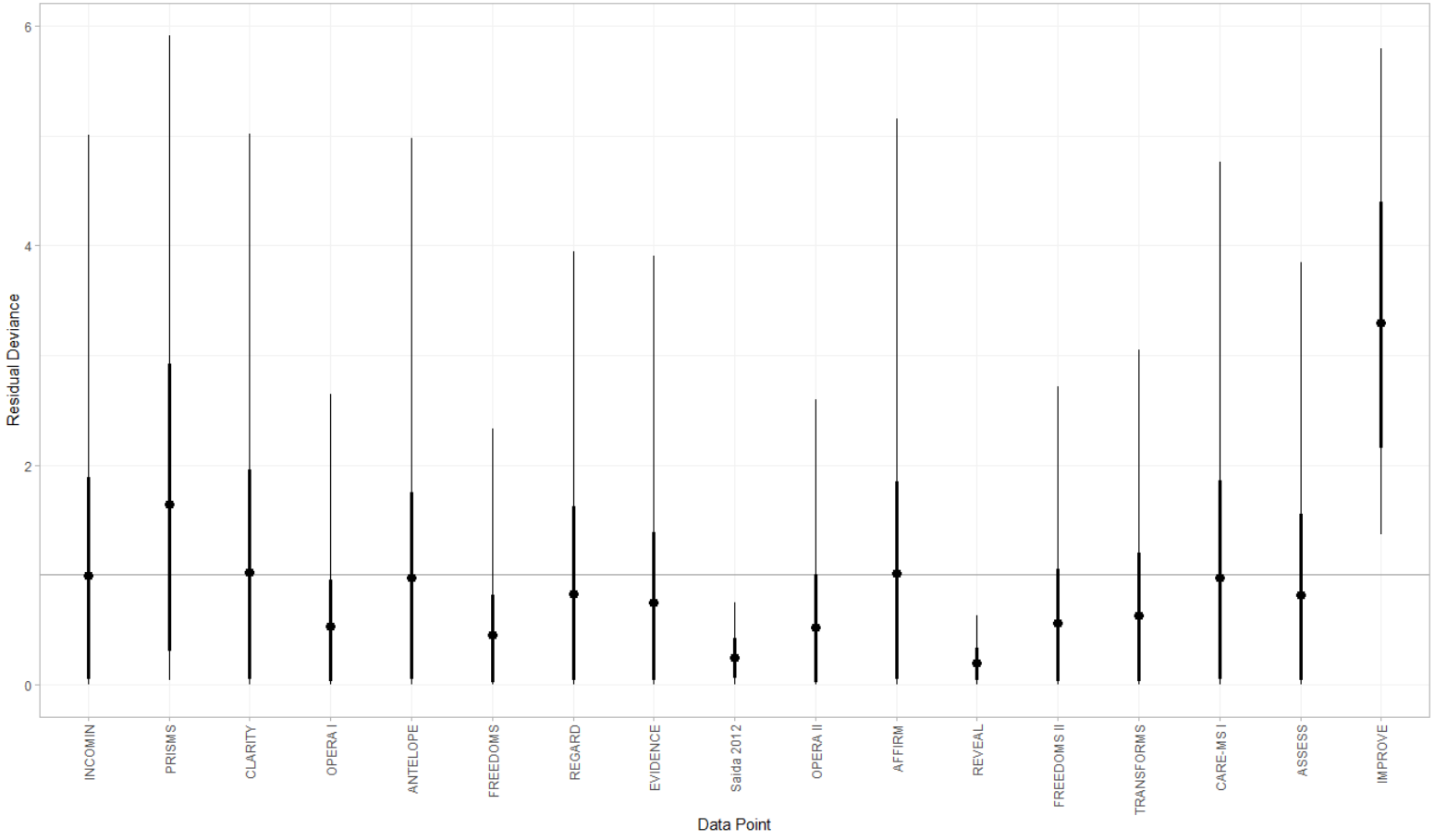

Table 77 Comparison (HR and 95% CrI) for each intervention pair for MRI T2 weighted lesions (fixed effects analysis; RRMS population)

	Placebo	Alemtuzumab IV12	Cladribine O3.5	Fingolimod O0.5	Glatiramer acetate SC20	Interferon beta 1a IM30	Interferon beta 1a SC22	Interferon beta 1a SC44	Interferon beta 1b IM 250	Natalizumab biosimilar	Natalizumab IV300
Alemtuzumab IV12	0.61 (0.45, 0.81)										
Cladribine O3.5	0.52 (0.43, 0.64)	0.86 (0.61, 1.23)									
Fingolimod O0.5	0.63 (0.55, 0.72)	1.04 (0.78, 1.40)	1.21 (0.96, 1.53)								
Glatiramer acetate SC20	0.80 (0.66, 0.98)	1.32 (0.99, 1.80)	1.53 (1.16, 2.03)	1.27 (1.07, 1.52)							
Interferon beta 1a IM30	0.77 (0.64, 0.92)	1.26 (0.95, 1.68)	1.46 (1.12, 1.92)	1.21 (1.03, 1.43)	0.95 (0.78, 1.17)						
Interferon beta 1a SC22	0.88 (0.71, 1.10)	1.45 (1.01, 2.09)	1.69 (1.25, 2.29)	1.40 (1.09, 1.79)	1.10 (0.83, 1.47)	1.15 (0.87, 1.52)					
Interferon beta 1a SC44	0.72 (0.61, 0.85)	1.19 (0.94, 1.50)	1.38 (1.06, 1.79)	1.14 (0.97, 1.34)	0.90 (0.75, 1.08)	0.94 (0.82, 1.09)	0.82 (0.62, 1.08)				
Interferon beta 1b IM 250	0.46 (0.29, 0.73)	0.76 (0.46, 1.29)	0.88 (0.52, 1.45)	0.73 (0.46, 1.15)	0.58 (0.36, 0.92)	0.60 (0.39, 0.92)	0.52 (0.31, 0.87)	0.64 (0.41, 1.00)			
Natalizumab biosimilar	0.46 (0.30, 0.70)	0.76 (0.46, 1.27)	0.88 (0.55, 1.41)	0.73 (0.47, 1.12)	0.57 (0.36, 0.90)	0.60 (0.38, 0.94)	0.52 (0.32, 0.83)	0.64 (0.41, 0.99)	1.00 (0.53, 1.83)		
Natalizumab IV300	0.50 (0.42, 0.59)	0.81 (0.58, 1.15)	0.94 (0.73, 1.22)	0.78 (0.64, 0.96)	0.62 (0.47, 0.79)	0.65 (0.50, 0.82)	0.56 (0.42, 0.74)	0.69 (0.54, 0.87)	1.07 (0.66, 1.75)	1.07 (0.73, 1.57)	
Ocrelizumab IV600	0.44 (0.36, 0.55)	0.73 (0.55, 0.96)	0.84 (0.63, 1.14)	0.70 (0.56, 0.86)	0.55 (0.44, 0.70)	0.58 (0.47, 0.71)	0.50 (0.37, 0.69)	0.61 (0.53, 0.71)	0.96 (0.60, 1.53)	0.96 (0.61, 1.55)	0.89 (0.68, 1.19)

Table 78 Probability that each intervention will rank in each position for MRI T2 weighted lesions (fixed effects analysis; RRMS population)

	p_rank[1]	p_rank[2]	p_rank[3]	p_rank[4]	p_rank[5]	p_rank[6]	p_rank[7]	p_rank[8]	p_rank[9]	p_rank[10]	p_rank[11]	p_rank[12]
Placebo	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.15	1.00
Alemtuzumab IV12	0.00	0.02	0.08	0.16	0.33	0.63	0.89	0.95	0.98	0.99	1.00	1.00
Cladribine O3.5	0.03	0.13	0.30	0.53	0.85	0.96	1.00	1.00	1.00	1.00	1.00	1.00
Fingolimod O0.5	0.00	0.00	0.00	0.01	0.11	0.51	0.94	0.99	1.00	1.00	1.00	1.00
Glatiramer acetate SC20	0.00	0.00	0.00	0.00	0.00	0.00	0.02	0.11	0.32	0.78	0.98	1.00
Interferon beta 1a IM30	0.00	0.00	0.00	0.00	0.00	0.00	0.04	0.21	0.63	0.92	1.00	1.00
Interferon beta 1a SC22	0.00	0.00	0.00	0.00	0.00	0.00	0.02	0.07	0.15	0.32	0.87	1.00
Interferon beta 1a SC44	0.00	0.00	0.00	0.00	0.00	0.02	0.14	0.70	0.94	0.99	1.00	1.00
Interferon beta 1b IM 250	0.32	0.50	0.62	0.74	0.86	0.93	0.97	0.99	0.99	1.00	1.00	1.00
Natalizumab biosimilar	0.31	0.49	0.65	0.78	0.88	0.95	0.98	0.99	0.99	1.00	1.00	1.00
Natalizumab IV300	0.04	0.20	0.49	0.81	0.96	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Ocrelizumab IV600	0.30	0.67	0.86	0.96	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00

Any AEs (RRMS population)

Table 79 Comparison of results from fixed and random effects NMA for any AEs (RRMS population)

	Fixed Effects	Random effects
Intervention	**HR (95% Credible interval)**	**HR (95% Credible interval)**
Alemtuzumab IV12	0.91 (0.55, 1.47)	0.91 (0.54, 1.51)
Cladribine O3.5	1.10 (0.94, 1.29)	1.10 (0.92, 1.31)
Fingolimod O0.5	1.02 (0.94, 1.11)	1.02 (0.93, 1.13)
Glatiramer acetate SC20	1.01 (0.90, 1.12)	1.01 (0.89, 1.14)
Glatiramer acetate SC40	1.06 (0.85, 1.30)	1.06 (0.83, 1.35)
Interferon beta 1a IM30	1.07 (0.93, 1.24)	1.07 (0.91, 1.25)
Interferon beta 1a SC44	0.88 (0.55, 1.40)	0.88 (0.54, 1.44)
Interferon beta 1b IM 250	0.77 (0.51, 1.19)	0.76 (0.49, 1.19)
Natalizumab biosimilar	0.92 (0.65, 1.28)	0.91 (0.64, 1.30)
Natalizumab IV300	0.97 (0.85, 1.11)	0.97 (0.83, 1.12)
Ocrelizumab IV600	0.88 (0.56, 1.38)	0.88 (0.55, 1.41)
Ofatumumab SC20	1.02 (0.73, 1.42)	1.03 (0.71, 1.49)
Peginterferon beta 1a SC125	1.12 (0.98, 1.27)	1.12 (0.97, 1.28)
Ponesimod O20	1.04 (0.77, 1.39)	1.04 (0.77, 1.42)
Teriflunomide O14	1.03 (0.74, 1.41)	1.03 (0.74, 1.47)
Tau (95% CrI)	NA	0.03 (0.002, 0.11)
Mean log odds ratio	-0.02	-0.02
Residual deviance:	17.8 (on 25 data points)	18.7 (on 25 data points)
pD	14.8	16.1
DIC	32.6	34.8

Note: the random effects model had good convergence (all Rhat <1.01) so informative priors were not needed.

Chosen model: Fixed effects model

Figure 35 Model fit for any AEs assessed by individual study residual deviance (fixed effects analysis; RRMS population)

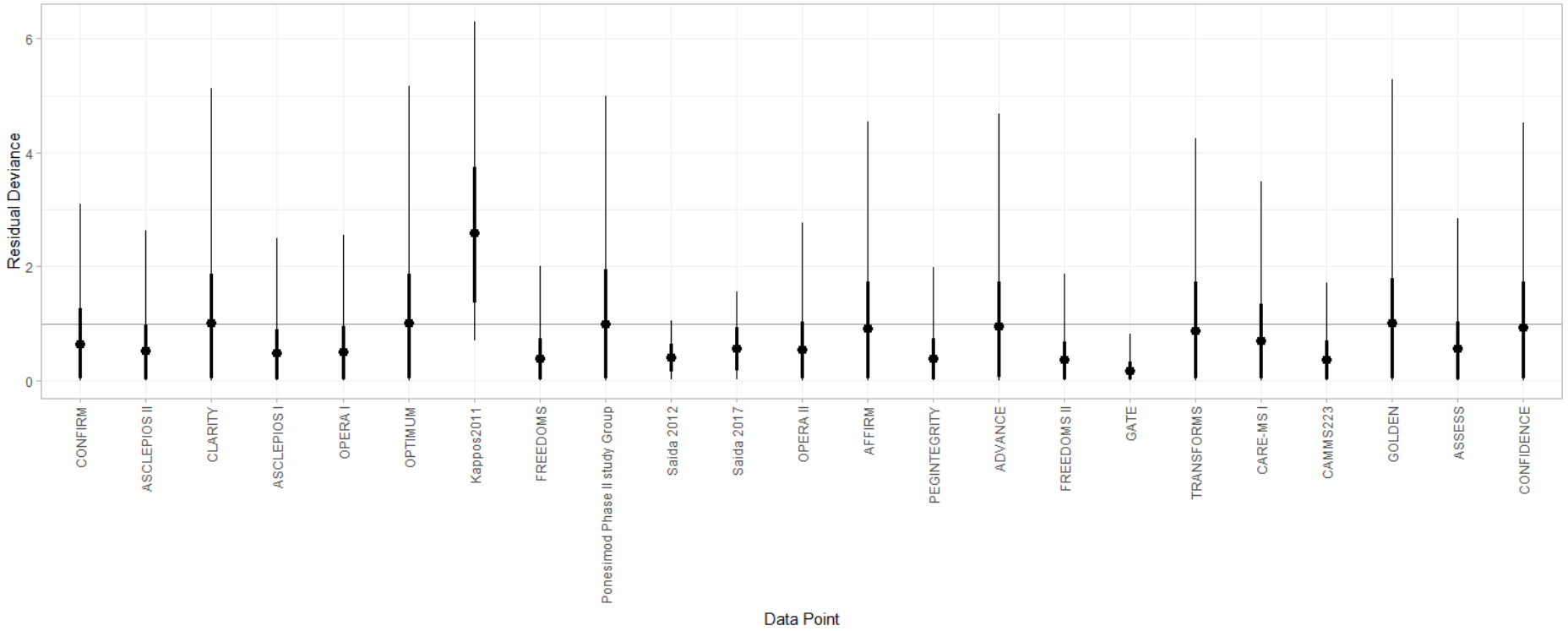

Table 80 Comparison (HR and 95% CrI) for each intervention pair for any AEs (fixed effects analysis; RRMS population)

	Placebo	Alemtuzumab IV12	Cladribine O3.5	Fingolimod O0.5	Glatiramer acetate SC20	Glatiramer acetate SC40	Interferon beta 1a IM30	Interferon beta 1a SC44	Interferon beta 1b IM 250	Natalizumab biosimilar	Natalizumab IV300	Ocrelizumab IV600	Ofatumumab SC20	Peginterferon beta 1a SC125	Ponesimod O20
Alemtuzumab IV12	0.91 (0.55, 1.47)														
Cladribine O3.5	1.10 (0.94, 1.29)	1.21 (0.73, 2.05)													
Fingolimod O0.5	1.02 (0.94, 1.11)	1.13 (0.69, 1.88)	0.93 (0.78, 1.11)												
Glatiramer acetate SC20	1.01 (0.90, 1.12)	1.11 (0.67, 1.86)	0.92 (0.76, 1.11)	0.99 (0.88, 1.11)											
Glatiramer acetate SC40	1.06 (0.85, 1.30)	1.16 (0.68, 2.00)	0.96 (0.74, 1.25)	1.03 (0.83, 1.27)	1.05 (0.87, 1.26)										
Interferon beta 1a IM30	1.07 (0.93, 1.24)	1.18 (0.71, 2.00)	0.98 (0.79, 1.20)	1.05 (0.92, 1.19)	1.06 (0.90, 1.25)	1.02 (0.79, 1.31)									
Interferon beta 1a SC44	0.88 (0.55, 1.40)	0.97 (0.83, 1.13)	0.80 (0.49, 1.30)	0.86 (0.54, 1.38)	0.87 (0.54, 1.41)	0.84 (0.50, 1.39)	0.82 (0.50, 1.33)								
Interferon beta 1b IM 250	0.77 (0.51, 1.19)	0.84 (0.43, 1.64)	0.70 (0.44, 1.10)	0.75 (0.50, 1.14)	0.76 (0.50, 1.17)	0.73 (0.45, 1.17)	0.71 (0.47, 1.11)	0.87 (0.46, 1.64)							
Natalizumab biosimilar	0.92 (0.65, 1.28)	1.01 (0.55, 1.85)	0.83 (0.57, 1.20)	0.90 (0.63, 1.27)	0.91 (0.63, 1.28)	0.87 (0.58, 1.29)	0.85 (0.59, 1.24)	1.04 (0.58, 1.86)	1.20 (0.68, 2.11)						
Natalizumab IV300	0.97 (0.85, 1.11)	1.07 (0.64, 1.80)	0.89 (0.73, 1.09)	0.95 (0.81, 1.11)	0.97 (0.81, 1.14)	0.92 (0.72, 1.18)	0.91 (0.75, 1.10)	1.10 (0.67, 1.80)	1.27 (0.80, 1.97)	1.06 (0.79, 1.45)					
Ocrelizumab IV600	0.88 (0.56, 1.38)	0.97 (0.81, 1.16)	0.80 (0.49, 1.29)	0.86 (0.54, 1.36)	0.87 (0.54, 1.39)	0.83 (0.50, 1.38)	0.82 (0.51, 1.31)	1.00 (0.90, 1.11)	1.15 (0.63, 2.14)	0.96 (0.54, 1.71)	0.90 (0.56, 1.45)				
Ofatumumab SC20	1.02 (0.73, 1.42)	1.13 (0.62, 2.02)	0.93 (0.65, 1.35)	1.00 (0.71, 1.40)	1.01 (0.71, 1.43)	0.97 (0.65, 1.45)	0.95 (0.66, 1.36)	1.16 (0.65, 2.05)	1.33 (0.77, 2.29)	1.12 (0.70, 1.77)	1.05 (0.74, 1.49)	1.16 (0.67, 2.05)			
Peginterferon beta 1a SC125	1.12 (0.98, 1.27)	1.23 (0.75, 2.08)	1.02 (0.84, 1.24)	1.09 (0.94, 1.27)	1.11 (0.93, 1.31)	1.06 (0.83, 1.36)	1.04 (0.88, 1.24)	1.27 (0.79, 2.09)	1.46 (0.93, 2.25)	1.22 (0.84, 1.77)	1.15 (0.96, 1.39)	1.27 (0.80, 2.05)	1.09 (0.77, 1.56)		
Ponesimod O20	1.04 (0.77, 1.39)	1.14 (0.65, 2.01)	0.94 (0.68, 1.31)	1.01 (0.74, 1.37)	1.03 (0.75, 1.40)	0.98 (0.68, 1.42)	0.97 (0.69, 1.33)	1.18 (0.68, 2.04)	1.35 (0.80, 2.28)	1.13 (0.73, 1.76)	1.07 (0.78, 1.47)	1.18 (0.68, 2.03)	1.01 (0.87, 1.19)	0.93 (0.67, 1.28)	
Teriflunomide O14	1.03 (0.74, 1.41)	1.13 (0.63, 2.01)	0.94 (0.66, 1.32)	1.01 (0.71, 1.41)	1.02 (0.73, 1.42)	0.97 (0.66, 1.42)	0.96 (0.68, 1.36)	1.17 (0.66, 2.04)	1.34 (0.79, 2.29)	1.12 (0.71, 1.77)	1.06 (0.75, 1.48)	1.17 (0.67, 2.04)	1.01 (0.92, 1.11)	0.92 (0.66, 1.30)	0.99 (0.88, 1.12)

Table 81 Probability that each intervention will rank in each position for any AEs (fixed effects analysis; RRMS population)

	p_rank[1]	p_rank[2]	p_rank[3]	p_rank[4]	p_rank[5]	p_rank[6]	p_rank[7]	p_rank[8]	p_rank[9]	p_rank[10]	p_rank[11]	p_rank[12]	p_rank[13]	p_rank[14]	p_rank[15]	p_rank[16]
Placebo	0.00	0.01	0.03	0.07	0.14	0.25	0.42	0.57	0.73	0.85	0.92	0.97	0.99	1.00	1.00	1.00
Alemtuzumab IV12	0.09	0.21	0.36	0.47	0.54	0.59	0.63	0.66	0.68	0.71	0.74	0.78	0.82	0.86	0.91	1.00
Cladribine O3.5	0.00	0.01	0.02	0.03	0.06	0.08	0.12	0.17	0.23	0.30	0.38	0.49	0.60	0.71	0.84	1.00
Fingolimod O0.5	0.00	0.01	0.02	0.05	0.10	0.17	0.27	0.39	0.52	0.65	0.78	0.87	0.94	0.98	1.00	1.00
Glatiramer acetate SC20	0.00	0.02	0.06	0.11	0.18	0.28	0.38	0.50	0.61	0.72	0.81	0.89	0.94	0.98	1.00	1.00
Glatiramer acetate SC40	0.01	0.04	0.07	0.11	0.17	0.23	0.29	0.34	0.41	0.47	0.54	0.61	0.70	0.79	0.88	1.00
Interferon beta 1a IM30	0.00	0.01	0.03	0.05	0.08	0.13	0.17	0.23	0.31	0.40	0.52	0.62	0.73	0.82	0.92	1.00
Interferon beta 1a SC44	0.09	0.29	0.47	0.56	0.61	0.66	0.69	0.72	0.75	0.78	0.81	0.84	0.87	0.92	0.97	1.00
Interferon beta 1b IM 250	0.49	0.58	0.63	0.76	0.82	0.85	0.87	0.89	0.91	0.92	0.94	0.95	0.96	0.97	0.98	1.00
Natalizumab biosimilar	0.14	0.30	0.36	0.44	0.57	0.62	0.66	0.72	0.75	0.78	0.82	0.85	0.88	0.91	0.94	1.00
Natalizumab IV300	0.01	0.06	0.15	0.23	0.35	0.50	0.59	0.68	0.77	0.83	0.88	0.92	0.96	0.98	1.00	1.00
Ocrelizumab IV600	0.10	0.26	0.44	0.56	0.63	0.67	0.70	0.73	0.75	0.79	0.82	0.85	0.88	0.94	0.98	1.00
Ofatumumab SC20	0.03	0.10	0.15	0.22	0.29	0.35	0.42	0.46	0.51	0.55	0.60	0.67	0.74	0.82	0.91	1.00
Peginterferon beta 1a SC125	0.00	0.00	0.01	0.01	0.02	0.04	0.06	0.09	0.14	0.20	0.29	0.40	0.54	0.67	0.83	1.00
Ponesimod O20	0.01	0.04	0.08	0.15	0.21	0.27	0.33	0.40	0.45	0.50	0.57	0.64	0.73	0.85	0.92	1.00
Teriflunomide O14	0.02	0.07	0.12	0.18	0.24	0.32	0.38	0.44	0.49	0.54	0.60	0.66	0.72	0.81	0.93	1.00

Serious Adverse Events (RRMS population)

Table 82 Comparison of results from fixed and random effects NMA for SAEs (RRMS population)

	Fixed Effects	Random effects
Intervention	**HR (95% Credible interval)**	**HR (95% Credible interval)**
Alemtuzumab IV12	1.06 (0.59, 1.90)	1.06 (0.55, 2.06)
Fingolimod O0.5	1.01 (0.78, 1.28)	1.02 (0.77, 1.39)
Glatiramer acetate SC20	0.83 (0.64, 1.07)	0.84 (0.63, 1.16)
Glatiramer acetate SC40	1.32 (0.51, 3.31)	1.35 (0.52, 3.58)
Interferon beta 1a IM30	0.92 (0.64, 1.32)	0.92 (0.61, 1.41)
Interferon beta 1a SC44	0.92 (0.59, 1.45)	0.92 (0.56, 1.54)
Interferon beta 1b IM 250	0.71 (0.48, 1.05)	0.71 (0.42, 1.18)
Natalizumab IV300	0.77 (0.58, 1.00)	0.75 (0.51, 1.05)
Ocrelizumab IV600	0.72 (0.41, 1.28)	0.72 (0.38, 1.41)
Ofatumumab SC20	1.58 (0.48, 4.99)	1.60 (0.47, 5.30)
Peginterferon beta 1a SC125	0.71 (0.50, 1.00)	0.71 (0.47, 1.12)
Ponesimod O20	1.46 (0.49, 4.22)	1.49 (0.50, 4.32)
Teriflunomide O14	1.37 (0.44, 4.15)	1.39 (0.43, 4.32)
Tau (95% CrI)	NA	0.11 (0.004, 0.32)
Mean log odds ratio	-0.01	-0.01
Residual deviance:	23.7 (on 31 data points)	23.1 (on 31 data points)
pD	13.1	14.8
DIC	36.8	37.8

Note: the random effects model had good convergence (all Rhat <1.01) so informative priors were not needed.

Chosen model: Fixed effects model

Figure 36 Model fit for SAEs assessed by individual study residual deviance (fixed effects analysis; RRMS population)

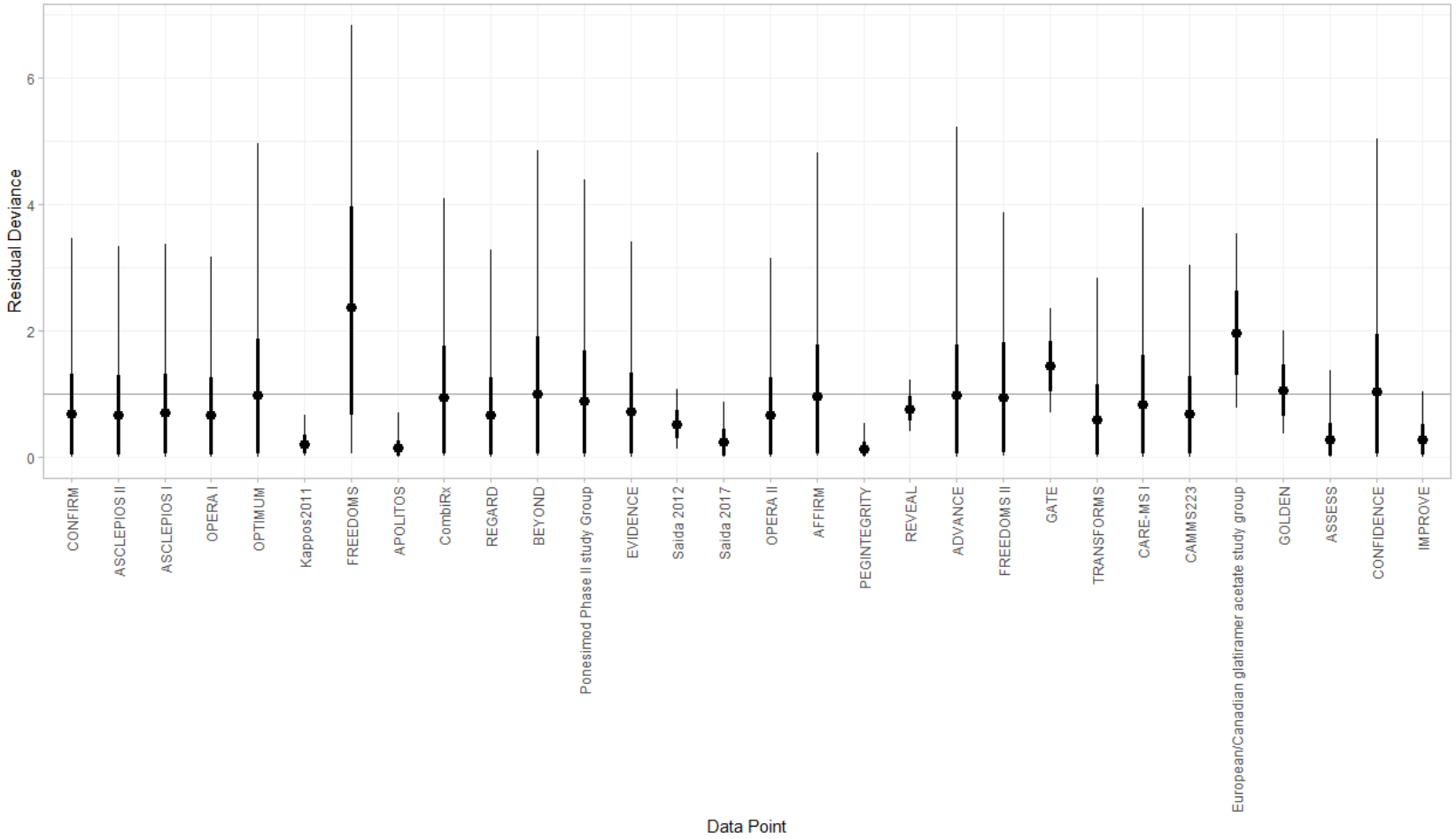

Table 83 Comparison (HR and 95% CrI) for each intervention pair for SAEs (fixed effects analysis; RRMS population)

	Placebo	Alemtuzumab IV12	Fingolimod O0.5	Glatiramer acetate SC20	Glatiramer acetate SC40	Interferon beta 1a IM30	Interferon beta 1a SC44	Interferon beta 1b IM 250	Natalizumab IV300	Ocrelizumab IV600	Ofatumumab SC20	Peginterferon beta 1a SC125
Alemtuzumab IV12	1.06 (0.59, 1.90)											
Fingolimod O0.5	1.01 (0.78, 1.28)	0.95 (0.53, 1.72)										
Glatiramer acetate SC20	0.83 (0.64, 1.07)	0.78 (0.45, 1.35)	0.82 (0.61, 1.12)									
Glatiramer acetate SC40	1.32 (0.51, 3.31)	1.25 (0.43, 3.50)	1.32 (0.52, 3.34)	1.60 (0.65, 3.98)								
Interferon beta 1a IM30	0.92 (0.64, 1.32)	0.86 (0.49, 1.56)	0.91 (0.63, 1.30)	1.11 (0.80, 1.55)	0.69 (0.26, 1.82)							
Interferon beta 1a SC44	0.92 (0.59, 1.45)	0.87 (0.61, 1.23)	0.92 (0.58, 1.48)	1.11 (0.74, 1.69)	0.70 (0.26, 1.87)	1.00 (0.65, 1.57)						
Interferon beta 1b IM 250	0.71 (0.48, 1.05)	0.67 (0.36, 1.24)	0.71 (0.46, 1.09)	0.86 (0.62, 1.18)	0.54 (0.20, 1.40)	0.77 (0.49, 1.22)	0.77 (0.45, 1.28)					
Natalizumab IV300	0.77 (0.58, 1.00)	0.72 (0.38, 1.38)	0.76 (0.54, 1.10)	0.93 (0.64, 1.36)	0.58 (0.22, 1.50)	0.83 (0.53, 1.33)	0.83 (0.48, 1.41)	1.08 (0.67, 1.75)				
Ocrelizumab IV600	0.72 (0.41, 1.28)	0.68 (0.41, 1.12)	0.72 (0.40, 1.29)	0.88 (0.51, 1.51)	0.55 (0.20, 1.55)	0.79 (0.44, 1.39)	0.79 (0.55, 1.11)	1.02 (0.55, 1.94)	0.95 (0.50, 1.79)			
Ofatumumab SC20	1.58 (0.48, 4.99)	1.48 (0.37, 5.34)	1.57 (0.47, 5.03)	1.91 (0.56, 6.01)	1.19 (0.26, 5.15)	1.72 (0.50, 5.74)	1.71 (0.47, 5.83)	2.22 (0.64, 7.43)	2.06 (0.61, 6.68)	2.17 (0.58, 7.86)		
Peginterferon beta 1a SC125	0.71 (0.50, 1.00)	0.67 (0.34, 1.30)	0.71 (0.47, 1.07)	0.86 (0.57, 1.31)	0.54 (0.20, 1.42)	0.77 (0.48, 1.26)	0.77 (0.44, 1.34)	1.00 (0.61, 1.64)	0.93 (0.60, 1.43)	0.98 (0.50, 1.90)	0.45 (0.13, 1.52)	
Ponesimod O20	1.46 (0.49, 4.22)	1.38 (0.39, 4.65)	1.46 (0.47, 4.28)	1.77 (0.57, 5.13)	1.11 (0.26, 4.50)	1.59 (0.50, 4.79)	1.59 (0.49, 5.05)	2.06 (0.64, 6.27)	1.91 (0.63, 5.75)	2.02 (0.60, 6.81)	0.93 (0.56, 1.53)	2.06 (0.66, 6.27)
Teriflunomide O14	1.37 (0.44, 4.15)	1.29 (0.35, 4.46)	1.36 (0.42, 4.26)	1.66 (0.50, 5.16)	1.03 (0.22, 4.37)	1.49 (0.44, 4.78)	1.49 (0.43, 4.83)	1.93 (0.58, 6.04)	1.79 (0.56, 5.59)	1.89 (0.52, 6.63)	0.87 (0.63, 1.18)	1.92 (0.59, 6.24)

Table 84 Probability that each intervention will rank in each position for SAEs (fixed effects analysis; RRMS population)

	p_rank[1]	p_rank[2]	p_rank[3]	p_rank[4]	p_rank[5]	p_rank[6]	p_rank[7]	p_rank[8]	p_rank[9]	p_rank[10]	p_rank[11]	p_rank[12]	p_rank[13]	p_rank[14]
Placebo	0.00	0.00	0.00	0.02	0.05	0.13	0.24	0.40	0.59	0.78	0.89	0.95	0.99	1.00
Alemtuzumab IV12	0.01	0.04	0.07	0.11	0.16	0.21	0.28	0.35	0.44	0.61	0.75	0.82	0.91	1.00
Fingolimod O0.5	0.00	0.01	0.02	0.04	0.09	0.16	0.26	0.40	0.57	0.76	0.86	0.93	0.98	1.00
Glatiramer acetate SC20	0.01	0.05	0.16	0.35	0.55	0.70	0.83	0.91	0.96	0.98	0.99	1.00	1.00	1.00
Glatiramer acetate SC40	0.05	0.08	0.10	0.12	0.16	0.19	0.22	0.26	0.30	0.36	0.56	0.62	0.70	1.00
Interferon beta 1a IM30	0.01	0.04	0.09	0.16	0.27	0.39	0.52	0.64	0.77	0.86	0.93	0.96	0.99	1.00
Interferon beta 1a SC44	0.00	0.04	0.11	0.19	0.29	0.40	0.52	0.63	0.76	0.85	0.91	0.96	1.00	1.00
Interferon beta 1b IM 250	0.23	0.44	0.60	0.72	0.80	0.88	0.92	0.95	0.97	0.99	0.99	1.00	1.00	1.00
Natalizumab IV300	0.10	0.27	0.44	0.57	0.69	0.79	0.87	0.93	0.96	0.98	0.99	1.00	1.00	1.00
Ocrelizumab IV600	0.28	0.42	0.54	0.64	0.72	0.79	0.85	0.90	0.94	0.96	0.98	0.99	1.00	1.00
Ofatumumab SC20	0.01	0.05	0.08	0.10	0.12	0.14	0.16	0.19	0.21	0.25	0.30	0.42	0.65	1.00
Peginterferon beta 1a SC125	0.23	0.43	0.58	0.70	0.79	0.86	0.91	0.95	0.97	0.99	0.99	1.00	1.00	1.00
Ponesimod O20	0.02	0.04	0.08	0.11	0.13	0.16	0.18	0.22	0.25	0.29	0.38	0.62	0.83	1.00
Teriflunomide O14	0.06	0.10	0.13	0.16	0.19	0.22	0.24	0.27	0.31	0.35	0.47	0.74	0.96	1.00

Discontinuation due to AEs (RRMS population)

Table 85 Comparison of results from fixed and random effects NMA for discontinuation due to AEs (RRMS population)

	Fixed Effects	Random effects
Intervention	**HR (95% Credible interval)**	**HR (95% Credible interval)**
Alemtuzumab IV12	0.42 (0.14, 1.14)	0.45 (0.13, 1.54)
Cladribine O3.5	1.68 (0.75, 3.78)	1.68 (0.56, 5.11)
Fingolimod O0.5	1.54 (1.16, 2.02)	1.63 (1.08, 2.64)
Glatiramer acetate SC20	2.15 (1.43, 3.27)	2.21 (1.25, 3.99)
Glatiramer acetate SC40	1.84 (1.00, 3.32)	1.86 (0.83, 4.16)
Interferon beta 1a IM30	1.53 (0.89, 2.59)	1.70 (0.87, 3.77)
Interferon beta 1a SC44	2.10 (1.19, 3.73)	2.29 (1.04, 5.29)
Interferon beta 1b IM 250	2.22 (1.04, 4.71)	2.41 (1.02, 6.19)
Natalizumab biosimilar	2.87 (0.67, 12.07)	2.63 (0.47, 14.21)
Natalizumab IV300	1.37 (0.75, 2.47)	1.27 (0.53, 2.85)
Ocrelizumab IV600	1.24 (0.59, 2.54)	1.37 (0.52, 3.88)
Peginterferon beta 1a SC125	3.48 (1.46, 8.36)	3.50 (1.24, 9.82)
Tau (95% CrI)	NA	0.27 (0.01, 0.69)
Mean log odds ratio	0.52	0.55
Residual deviance:	29.2 (on 28 data points)	26 (on 28 data points)
pD	12	15.7
DIC	41.2	41.7

Note: the random effects model had good convergence (all Rhat <1.01) so informative priors were not needed.

Chosen model: Fixed effects model

Figure 37 Model fit for discontinuation due to AEs assessed by individual study residual deviance (fixed effects analysis; RRMS population)

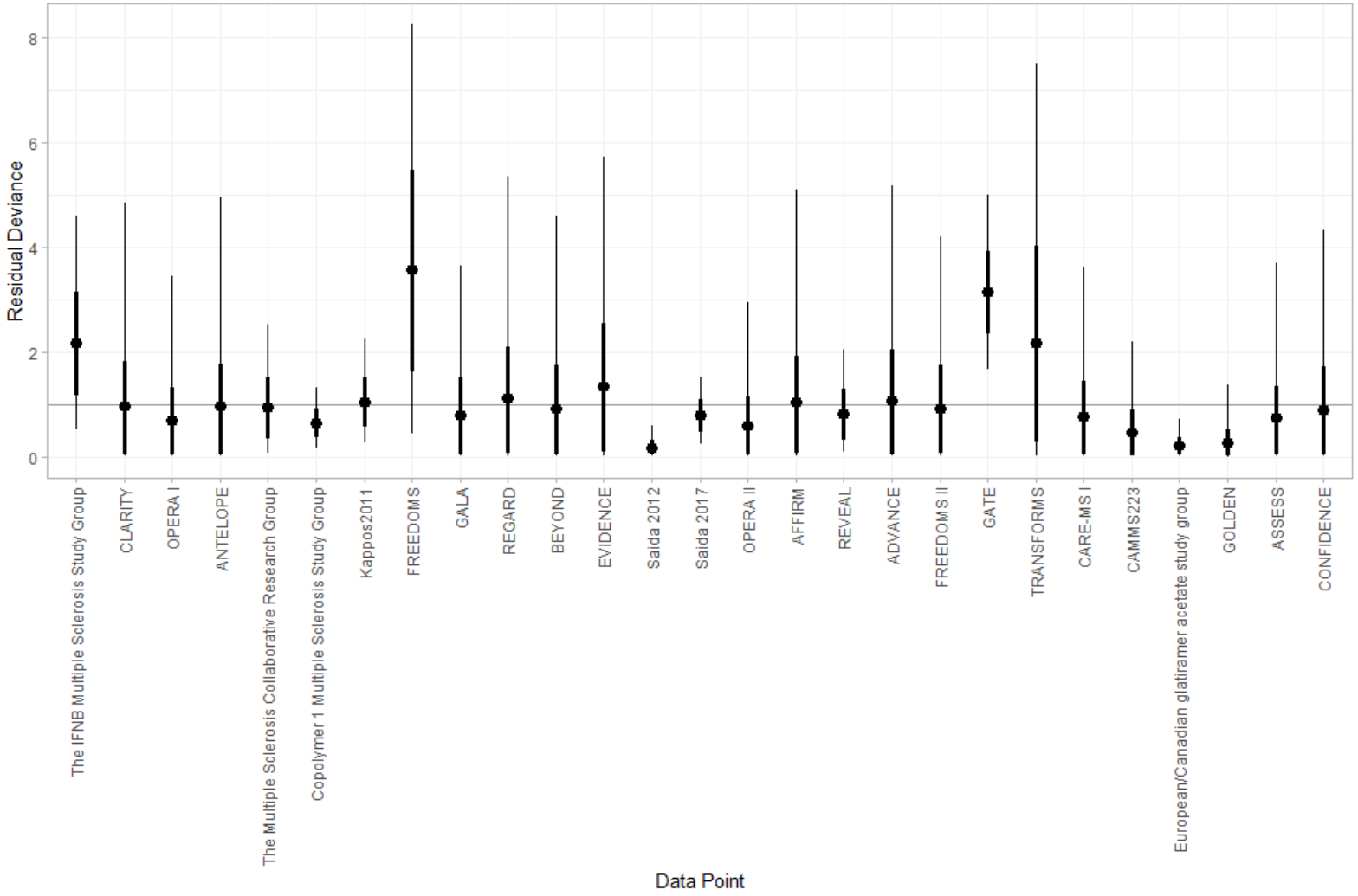

Table 86 Comparison (RR and 95% CrI) for each intervention pair for discontinuation due to AEs (fixed effects analysis; RRMS population)

	Placebo	Alemtuzumab IV12	Cladribine O3.5	Fingolimod O0.5	Glatiramer acetate SC20	Glatiramer acetate SC40	Interferon beta 1a IM30	Interferon beta 1a SC44	Interferon beta 1b IM 250	Natalizumab biosimilar	Natalizumab IV300	Ocrelizumab IV600
Alemtuzumab IV12	0.42 (0.14, 1.14)											
Cladribine O3.5	1.68 (0.75, 3.78)	4.04 (1.14, 14.59)										
Fingolimod O0.5	1.54 (1.16, 2.02)	3.71 (1.37, 10.17)	0.92 (0.39, 2.16)									
Glatiramer acetate SC20	2.15 (1.43, 3.27)	5.18 (1.86, 14.34)	1.28 (0.53, 3.21)	1.40 (0.97, 2.00)								
Glatiramer acetate SC40	1.84 (1.00, 3.32)	4.42 (1.39, 13.89)	1.09 (0.40, 2.96)	1.19 (0.65, 2.21)	0.85 (0.47, 1.52)							
Interferon beta 1a IM30	1.53 (0.89, 2.59)	3.67 (1.28, 10.45)	0.91 (0.36, 2.36)	0.99 (0.58, 1.61)	0.71 (0.41, 1.22)	0.83 (0.40, 1.74)						
Interferon beta 1a SC44	2.10 (1.19, 3.73)	5.06 (2.16, 12.11)	1.25 (0.49, 3.42)	1.36 (0.79, 2.36)	0.98 (0.58, 1.64)	1.15 (0.55, 2.39)	1.38 (0.81, 2.31)					
Interferon beta 1b IM 250	2.22 (1.04, 4.71)	5.35 (1.55, 18.48)	1.33 (0.46, 3.99)	1.44 (0.69, 3.00)	1.03 (0.52, 2.10)	1.21 (0.49, 2.97)	1.46 (0.63, 3.32)	1.06 (0.45, 2.43)				
Natalizumab biosimilar	2.87 (0.67, 12.07)	6.91 (1.14, 42.03)	1.71 (0.33, 8.88)	1.86 (0.44, 8.19)	1.33 (0.31, 5.82)	1.56 (0.35, 7.52)	1.88 (0.44, 9.02)	1.36 (0.30, 6.44)	1.29 (0.26, 6.37)			
Natalizumab IV300	1.37 (0.75, 2.47)	3.30 (1.00, 11.22)	0.82 (0.30, 2.24)	0.89 (0.46, 1.74)	0.64 (0.32, 1.30)	0.75 (0.32, 1.74)	0.90 (0.40, 2.04)	0.65 (0.29, 1.48)	0.62 (0.24, 1.62)	0.48 (0.13, 1.76)		
Ocrelizumab IV600	1.24 (0.59, 2.54)	2.97 (1.15, 7.98)	0.74 (0.25, 2.19)	0.80 (0.40, 1.63)	0.57 (0.29, 1.12)	0.67 (0.29, 1.58)	0.81 (0.42, 1.62)	0.59 (0.38, 0.94)	0.56 (0.22, 1.43)	0.43 (0.09, 2.06)	0.90 (0.35, 2.29)	
Peginterferon beta 1a SC125	3.48 (1.46, 8.36)	8.38 (2.24, 31.99)	2.08 (0.63, 6.89)	2.26 (0.90, 5.66)	1.62 (0.62, 4.43)	1.90 (0.66, 5.66)	2.28 (0.83, 6.29)	1.66 (0.58, 4.76)	1.57 (0.50, 5.00)	1.21 (0.22, 6.28)	2.54 (0.90, 7.53)	2.82 (0.92, 8.82)

Table 87 Probability that each intervention will rank in each position for discontinuation due to AEs (fixed effects analysis; RRMS population)

	p_rank[1]	p_rank[2]	p_rank[3]	p_rank[4]	p_rank[5]	p_rank[6]	p_rank[7]	p_rank[8]	p_rank[9]	p_rank[10]	p_rank[11]	p_rank[12]	p_rank[13]
Placebo	0.03	0.49	0.84	0.96	0.99	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Alemtuzumab IV12	0.92	0.97	0.98	0.99	0.99	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Cladribine O3.5	0.01	0.09	0.17	0.27	0.36	0.45	0.53	0.62	0.70	0.79	0.88	0.97	1.00
Fingolimod O0.5	0.00	0.00	0.04	0.15	0.37	0.60	0.81	0.92	0.98	0.99	1.00	1.00	1.00
Glatiramer acetate SC20	0.00	0.00	0.00	0.00	0.01	0.03	0.10	0.22	0.44	0.69	0.89	0.98	1.00
Glatiramer acetate SC40	0.00	0.01	0.05	0.12	0.21	0.31	0.42	0.56	0.69	0.81	0.92	0.98	1.00
Interferon beta 1a IM30	0.00	0.03	0.11	0.26	0.42	0.58	0.73	0.84	0.92	0.97	0.99	1.00	1.00
Interferon beta 1a SC44	0.00	0.00	0.00	0.02	0.05	0.11	0.20	0.33	0.49	0.67	0.85	0.97	1.00
Interferon beta 1b IM 250	0.00	0.01	0.03	0.07	0.11	0.17	0.24	0.32	0.43	0.56	0.74	0.91	1.00
Natalizumab biosimilar	0.01	0.06	0.09	0.13	0.17	0.21	0.24	0.28	0.33	0.39	0.46	0.65	1.00
Natalizumab IV300	0.01	0.11	0.27	0.44	0.58	0.70	0.79	0.86	0.92	0.96	0.99	1.00	1.00
Ocrelizumab IV600	0.01	0.23	0.41	0.58	0.71	0.80	0.88	0.93	0.97	0.98	1.00	1.00	1.00
Peginterferon beta 1a SC125	0.00	0.00	0.01	0.01	0.03	0.04	0.07	0.10	0.13	0.18	0.28	0.55	1.00

ARR (HARR MS population)

Table 88 Comparison of results from fixed and random effects NMA for ARR (HARRMS population)

	Fixed Effects	Random effects
Intervention	**RR (95% Credible interval)**	**RR (95% Credible interval)**
Alemtuzumab IV12	0.53 (0.30, 0.92)	0.64 (0.00, 200.49)
Cladribine O3.5	0.57 (0.33, 0.97)	0.57 (0.02, 22.18)
Fingolimod O0.5	0.52 (0.39, 0.69)	0.56 (0.02, 18.53)
Interferon beta 1a	1.03 (0.64, 1.67)	1.23 (0.02, 143.02)
Natalizumab IV300	0.31 (0.15, 0.63)	0.32 (0.01, 11.88)
Ocrelizumab IV600	0.33 (0.15, 0.69)	0.38 (0.00, 102.99
Tau (95% CrI)	NA	1.40 (0.05,3.95)
Mean log odds ratio	-0.69	-0.58
Residual deviance:	8.1 (on 8 data points)	8 (on 8 data points)
pD	8.1	8
DIC	16.2	16.1

Note: all Rhat <1.01

RE parameters:

seed	437219664
trt_effects	"random"
prior_intercept	normal(0, scale = 10)
prior_trt	normal(0, scale = 5)
prior_het	half_normal(scale = 2)
control = list	max_treedepth = 12
adapt_delta	0.99

Chosen model: Fixed effects model

Figure 38 Model fit for ARR assessed by individual study residual deviance (fixed effects analysis; HARRMS population)

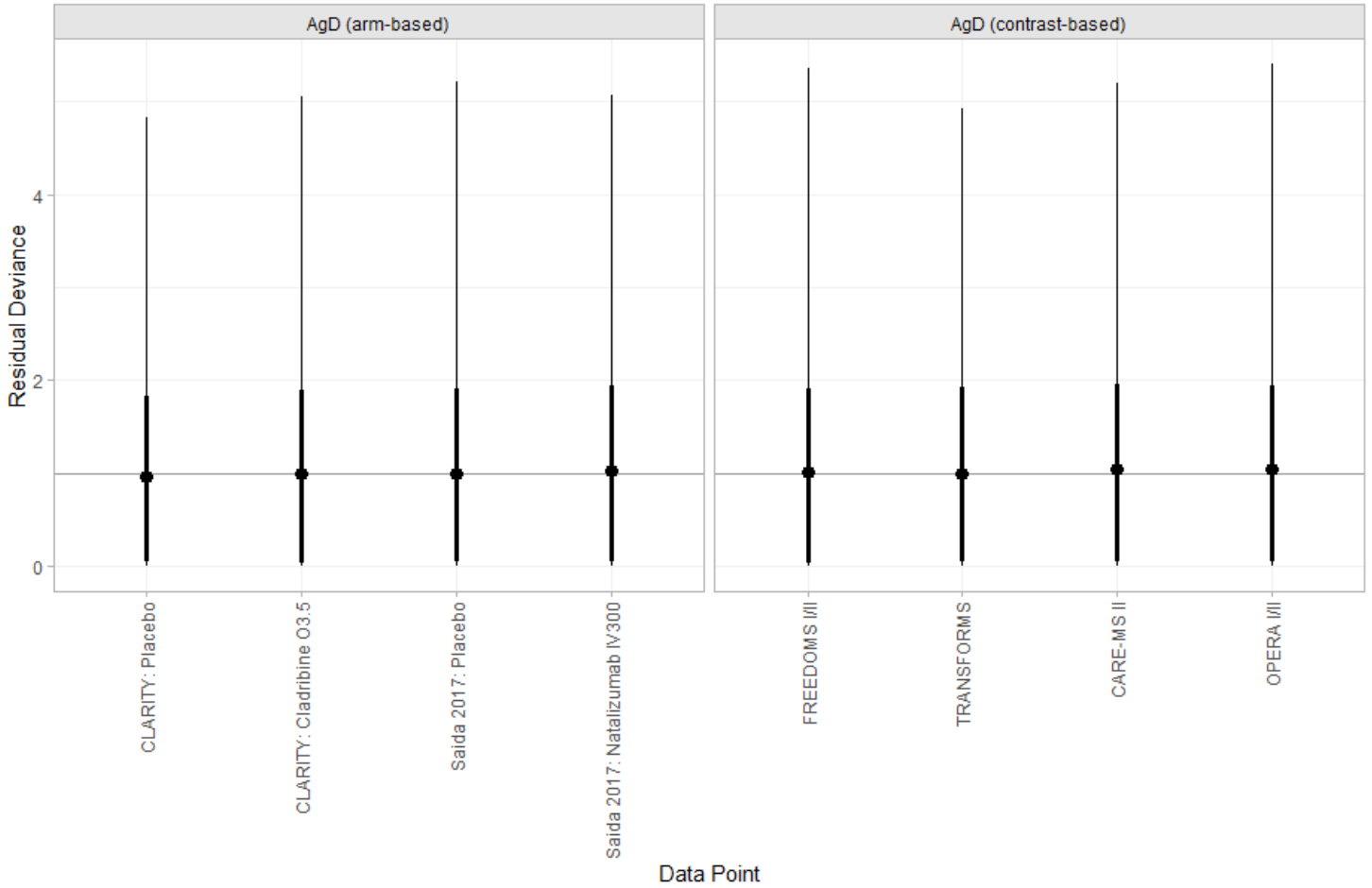

Table 89 Comparison (RR and 95% CrI) for each intervention pair for ARR (random effects analysis; HARRMS population)

	Placebo	Alemtuzumab IV12	Cladribine O3.5	Fingolimod O0.5	Interferon beta 1a	Natalizumab IV300
Alemtuzumab IV12	0.53 (0.30, 0.92)					
Cladribine O3.5	0.57 (0.33, 0.97)	1.08 (0.49, 2.39)				
Fingolimod O0.5	0.52 (0.39, 0.69)	0.99 (0.61, 1.60)	0.91 (0.50, 1.69)			
Interferon beta 1a	1.03 (0.64, 1.67)	1.97 (1.52, 2.56)	1.82 (0.87, 3.83)	1.99 (1.33, 2.97)		
Natalizumab IV300	0.31 (0.15, 0.63)	0.59 (0.24, 1.43)	0.54 (0.22, 1.39)	0.59 (0.28, 1.29)	0.30 (0.13, 0.70)	
Ocrelizumab IV600	0.33 (0.15, 0.69)	0.62 (0.33, 1.17)	0.58 (0.23, 1.43)	0.63 (0.31, 1.29)	0.32 (0.18, 0.56)	1.06 (0.38, 3.00)

Table 90 Probability that each intervention will rank in each position for ARR (random effects analysis; HARRMS population)

	p_rank[1]	p_rank[2]	p_rank[3]	p_rank[4]	p_rank[5]	p_rank[6]	p_rank[7]
Placebo	0.00	0.00	0.00	0.00	0.02	0.57	1.00
Alemtuzumab IV12	0.01	0.12	0.43	0.70	0.99	1.00	1.00
Cladribine O3.5	0.02	0.13	0.33	0.53	0.94	0.99	1.00
Fingolimod O0.5	0.00	0.09	0.39	0.83	1.00	1.00	1.00
Interferon beta 1a	0.00	0.00	0.00	0.00	0.05	0.45	1.00
Natalizumab IV300	0.53	0.83	0.92	0.96	1.00	1.00	1.00
Ocrelizumab IV600	0.44	0.84	0.93	0.97	1.00	1.00	1.00

Appendix 6
Details on economic models in previous relevant TAs

Table 91 Summary of economic evaluations of Highly Active Relapse Remitting Multiple Sclerosis technologies with marketing authorisation in the UK

TA (year) Intervention	Model type	Time horizon	Discount Rate	Population	Comparators	Outcomes and sources of data
TA767 (2022) Ponesimod (Ponvory, Janssen)[42]	Markov Cohort Model	Lifetime 50 years (annual cycles)	3.5 %	RRMS *Subgroup:* HA RRMS	RRMS • Beta interferons, • Dimethyl fumarate, • Glatiramer acetate, • Teriflunomide, • Ocrelizumab, • Peginterferon beta-1a • Ofatumumab. HA RRMS • Alemtuzumab • Fingolimod • Cladribine, • Ofatumumab and • Ocrelizumab (only if alemtuzumab is contraindicated or otherwise unsuitable)	Intervention: ARR, CDP-3, CDP-6, AEs from OPTIMUM, OPTIMUM-LT Comparators: ARR, DCP-3, CDP-6, All cause discontinuation from NMA (RRMS), NMA (HA RRMS) Natural History: RRMS transitions from the British Columbia Multiple Sclerosis registry,[126] HA RRMS transitions from the AFFIRM trial. Converting from RRMS to SPMS from the London, Ontario MS database.[127] ARR by EDSS[127] Relative risk of relapse from the AFFIRM trial. Relative risk of death applied to EDSS states.[337]

TA (year) Intervention	Model type	Time horizon	Discount Rate	Population	Comparators	Outcomes and sources of data
TA699 (2021) Ofatumumab (Kesimpta, Novartis)[41]	Markov Cohort Model	Lifetime 62 years (annual cycles)	3.5 %	RRMS *Subgroups:* HA RRMS & RES RRMS were not considered suitable for decision making	RRMS • Beta interferons, • Dimethyl fumarate, • Glatiramer acetate, • Teriflunomide, • Peginterferon beta-1a	Intervention: ARR, CDP-3, CDP-6, AEs , EQ-5D from ASCLEPIOS I, ASCLEPIOS II Comparators: ARR, DCP-3, CDP-6, All cause discontinuation from NMA (RRMS) Natural History: RRMS transitions from the British Columbia Multiple Sclerosis registry,[126]. Converting from RRMS to SPMS from the London, Ontario MS database[127] supplemented by the EXPAND trial. ARR by EDSS[127] Relative risk of relapse from the AFFIRM trial. Relative risk of death applied to EDSS states.[337]
TA616 (2019) Cladribine tablets (Mavenclad, Merck Serono)[38]	Markov Cohort Model	Lifetime 50 years (annual cycles)	3.5 %	RES RRMS SOT RRMS	RES RRMS • Alemtuzumab • Natalizumab • Daclizumab (contra indicated to alemtuzumab) SOT RRMS • Alemtuzumab • Fingolimod • Daclizumab (contra indicated to alemtuzumab)	Intervention & Comparators relative treatment effects: ARR, DCP-3, CDP-6, relapse free patients, AEs (grades 3 or 4), discontinuation due to AEs, all cause discontinuation from NMA & Meta-regressions per sub-group (RES RRMS, SOT RRMS) Intervention: EQ-5D from ASCLEPIOS I Natural History: RRMS transitions from the British Columbia Multiple Sclerosis registry,[126]. Faster rates of progression for the SOT RRMS & RES RRMS groups based on CLARITY. Converting from RRMS to SPMS from the London, Ontario MS database[127] supplemented by the EXPAND trial. ARR independent of EDSS, year1 pbo arm of CLARITY, subsequent years as a function of time from the British Columbia Multiple Sclerosis registry.[170] Relative risk of death from a meta-analysis of SMRs.[338]

TA (year) Intervention	Model type	Time horizon	Discount Rate	Population	Comparators	Outcomes and sources of data
TA533 (2018) Ocrelizumab (Ocrevus, Roche)[33]	Multi-state Markov Cohort Model	Lifetime 50 years (annual cycles)	3.5 %	RRMS *Subgroups:* HA RRMS RES RRMS	RRMS • Alemtuzumab, • Beta interferons, • Dimethyl fumarate, • Glatiramer acetate, • Natalizumab, • Fingolimod. HA RRMS • Alemtuzumab • Fingolimod RES RRMS • Alemtuzumab • Natalizumab	Intervention: ARR, DCP-3, CDP-6, AEs, EQ-5D from OPERA I - OPERA II - OPERA OLE Comparators: ARR, DCP-3, CDP-6, All cause discontinuation, NMA (RRMS) - NMA (HA RRMS) - NMA (RES RRMS) Natural History: RRMS transitions from the British Columbia Multiple Sclerosis registry,[126] HA RRMS transitions from the AFFIRM trial. Converting from RRMS to SPMS from the London, Ontario MS database.[127] ARR by EDSS.[127] Relative risk of relapse from the AFFIRM trial. Relative risk of death applied to EDSS states[337]
TA312 (2014, update 2020) Alemtuzumab (Lemtrada, Sanofi)[39]	Multi-state Markov Cohort Model	Lifetime 50 years (annual cycles)	3.5 %	RRMS *Subgroups:* HA RRMS RES RRMS	RRMS • Beta interferons, • Glatiramer acetate, HA RRMS • Fingolimod RES RRMS • Natalizumab	Intervention & Comparators relative treatment effects: ARR, SAD-3, SAD-6, relapse free patients, discontinuation due to AEs from NMAs per group / sub-group (RRMS, HA RRMS and RES RRMS) Intervention: AEs, SAEs, EQ-5D from CAMMS223, CARE-MS I & II Natural History: RRMS transitions EDSS (1-9) and converting from RRMS to SPMS were sourced from the London Ontario MS database.[127] RRMSEDSS 0 from the placebo arms of TOWER & TEMSO trials ARR by EDSS[127] Relative risk of death applied to EDSS states[337]

TA (year) Intervention	Model type	Time horizon	Discount Rate	Population	Comparators	Outcomes and sources of data
TA254 (2012) Fingolimod (Gilenya, Novartis)[40]	Markov Cohort Model	Lifetime 50 years (annual cycles)	3.5 %	Main analysis: 1b)HA RRMS In DP not in CE analysis: 1a)HA RRMS 2)RES RRMS	1b)HA RRMS • beta interferon-1a (Avonex) • Rebif-22 • Rebif-44 • Betaferon • Extavia	Intervention ARR, SAD-3, SAD-6 from the TRANSFORMS & FREEDOMS trials. Comparators: ARR, SAD-3, SAD-6 from NMAs (HA RRMS) Natural History: RRMS transitions EDSS (1-9) and converting from RRMS to SPMS from the London, Ontario MS database .[115] ARR by EDSS[127] Relative risk of death applied to EDSS states.[337]
TA127 (2007) (Tysabri, Biogen Inc)[34]	Multi-state Markov Cohort Model	Lifetime 20 years (annual cycles)	3.5 %	RES RRMS SOT RRMS	• Beta interferons, • Glatiramer acetate.	Intervention ARR, SAD-3, SAD-6 from AFFIRM. Comparators: ARR, SAD-3, SAD-6 from pairwise meta-analyses Natural History: RRMS transitions EDSS (1-9) and converting from RRMS to SPMS from the London, Ontario MS database .[115] } HA RRMS transitions from the AFFIRM trial. ARR by EDSS[127] Relative risk of death applied to EDSS states[337]

Table 92 (continued) Summary of economic evaluations of Highly Active Relapse Remitting Multiple Sclerosis technologies with marketing authorisation in the UK

TA, year	Health states	Utilities & Costs	EAG key Criticism	Results
TA767 (2022) Ponesimod (Ponvory, Janssen)[42]	20 in total: • 10 EDSS RRMS • 9 EDSS SPMS • Death	• RRMS EQ-5D EDSS 0-9, • SPMS Utility decrement • Caregiver disutilities • Relapse HS disutilities • AE utility decrements • Drug acquisition, administration and monitoring costs • HS Costs EDSS 0-9, • AE Costs	**Treatment switching or sequencing** – The EAG acknowledged the availability of data a limitation on modelling this aspect of clinical practice, leading to an oversimplified model. **Implausible no. of patients in high EDSS states** – Contrary to the expert opinion of clinical advisors a higher proportion of patients than would be observed in practice progressed to EDSS 8 and 9 where they accumulated negative QALYs. The EAG was critical of this aspect of the model, despite it being broadly in line with other appraisals. The committee concluded that this model, as with other multiple sclerosis models, was limited in its ability to accurately reflect the course of the condition. **More appropriate data on mortality** - Clinical experts considered the mortality data was outdated and that managing acute infection and nursing has fundamentally reduced mortality with MS. That new standardised mortality rates by EDSS state had been recently published. The committee concluded that in future appraisals in MS, it would like to see more appropriate sources of mortality data in a model with plausible distributions of people in EDSS states.	The committee concluded that overall, the cost-effectiveness results were acceptable and the most likely estimates were below what NICE considers an acceptable use of NHS resources
TA699 (2021) Ofatumumab (Kesimpta, Novartis)[41]	21 in total: • 10 EDSS RRMS • 10 EDSS SPMS	• RRMS EQ-5D EDSS 0-9, • SPMS Utility decrement	**loss of treatment effectiveness** – The committee refereed to TA533 (Ocrelizumab) which had accepted treatment discontinuation as proxy for loss of effectiveness over time, despite lack of evidence on waning from the key trials.	The committee referred to the appraisal guidelines stating that, above a most plausible ICER of £20,000 per quality-adjusted life year (QALY) gained, judgements about the acceptability of a technology as an effective use of NHS resources

TA, year	Health states	Utilities & Costs	EAG key Criticism	Results
	• Death	• Caregiver disutilities • Relapse HS disutilities • AE utility decrements • Drug acquisition, administration and monitoring costs • HS Costs EDSS 0-9, • AE Costs	**Implausible relapse rates in higher EDSS states** – Contrary to clinical advice the company modelled increasing relapse rates at the higher EDSS SPMS states. The EAG went with values that were decreasing as severity increased, reported in TA 527. **Conflicting approaches to converting from RRMS to SPMS** – the company used transition matrices from the British Columbia longitudinal multiple sclerosis dataset (TA254). The EAG preferred to use transition matrices from the London Ontario multiple sclerosis dataset (TA624) Both data sources had been accepted previously by NICE technology appraisal committees and were found to have minimal impact on the ICERs.	will take into account the degree of certainty around the ICER. The committee noted that, with the exception of waning of treatment effect, changes to each assumption had a minor impact on the base-case ICER. The committee concluded that it could recommend ofatumumab as an additional treatment option for relapsing–remitting multiple sclerosis.
TA616 (2019) Cladribine tablets (Mavenclad, Merck Serono)[38]	21 in total: • 10 EDSS RRMS • 10 EDSS SPMS • Death	• RRMS EQ-5D EDSS 0-9, • SPMS Utility decrement • Caregiver disutilities • Relapse HS disutilities • AE utility decrements • Drug acquisition, administration and monitoring costs • HS Costs EDSS 0-9, • AE Costs	**Inaccurate RES RRMS & SOT RRMS natural history** - The company calculating different rates of disability progression in the subgroups. The clinical experts and the EAG explained that, although assuming different rates of disease progression for each subgroup was reasonable, the company's approach was simplistic and potentially inaccurate. The committee appreciated that there was no clear alternative data source or method, and was aware that such adjustment had not been used in previous technology appraisals. **loss of treatment effectiveness** – The company used treatment switching analysis to support their assumption; treatment waning for Cladribine to begin 2 years later than comparators. The committee noted that there was no statistically significant evidence to support different waning effects and that patient numbers used for the analysis in the subgroups were very small. It concluded that the company's evidence	Cladribine dominated all other treatments in both RES RRMS and SOT RRMS groups. Cladribine was more effective and cheaper than fingolimod and natalizumab. It was less effective and cheaper than alemtuzumab. The ICERs vs. alemtuzumab were: • £219,549 gained per QALY lost (RES RRMS) • £372,802 gained per QALY lost SOT (RRMS) The committee concluded that cladribine was a cost-effective use of NHS resources for rapidly evolving severe relapsing–remitting multiple sclerosis and sub optimally treated relapsing–remitting multiple sclerosis.

TA, year	Health states	Utilities & Costs	EAG key Criticism	Results
			was insufficient to justify using a different treatment waning assumption for cladribine. **Treatment stopping rates are not constant** - The EAG explained that people are more likely to stop treatment during the first year of treatment than in a subsequent year. Therefore, the company's approach of applying trial-based discontinuation rates to subsequent years would overestimate the number of people stopping treatment.	
TA533 (2018) Ocrelizumab (Ocrevus, Roche)[33]	31 in total: • 20 EDSS RRMS • 10 EDSS SPMS • Death	• RRMS EQ-5D EDSS 0-9, • SPMS Utility decrement • Caregiver disutilities • Relapse HS disutilities • AE utility decrements • Drug acquisition, administration and monitoring costs • HS Costs EDSS 0-9, • AE Costs	**loss of treatment effectiveness** – In clinical practice, when a drug is no longer effective, patients switch on to alternative treatments. Treatment switching was not included in the model. The EAG accepted treatment discontinuation as proxy for loss of effectiveness over time, despite lack of evidence on waning from the key trials.	The most plausible ICERs were below £30,000 per QALY gained in the relapsing–remitting multiple sclerosis population compared with all relevant comparators, apart from alemtuzumab, which dominated all comparisons. In the highly active subgroup, the most plausible ICER for ocrelizumab compared with fingolimod was below £20,000 per QALY gained. In the rapidly evolving severe subgroup, ocrelizumab was cheaper and less effective than natalizumab. The most plausible ICER for ocrelizumab compared with natalizumab was In the range of £350,000 to £125,000 saved per QALY lost .
TA312 (2014, update 2020) Alemtuzumab (Lemtrada, Sanofi)[39]	20 in total: • 10 EDSS RRMS • 9 EDSS SPMS	• RRMS EQ-5D EDSS 0-9, • SPMS Utility decrement	**loss of treatment effectiveness** – The company assumed treatment with Alemtuzumab would persist indefinitely. The clinical specialists also stated that people who experience a relapse soon after treatment with	The most plausible ICER for alemtuzumab compared with glatiramer acetate for people with active relapsing-remitting multiple sclerosis is likely to lie between £13,600

TA, year	Health states	Utilities & Costs	EAG key Criticism	Results
	• Death	• Caregiver disutilities • Relapse HS disutilities • AE utility decrements • Drug acquisition, administration and monitoring costs • HS Costs EDSS 0-9, • AE Costs	alemtuzumab will probably be offered alternative treatment. The Committee stated that, for some people, alemtuzumab might not provide long-term enduring effect and other treatments might be required. The Committee concluded that because of the uncertainty about the long-term treatment effects it was appropriate to incorporate waning effects into the model.	and £24,500 per QALY gained active relapsing–remitting multiple sclerosis. The most plausible ICER for patients with highly active relapsing-remitting multiple sclerosis despite beta interferon treatment was £8900 per QALY gained for alemtuzumab compared with fingolimod. Alemtuzumab dominated natalizumab (that is, less expensive and more effective) for patients with rapidly evolving severe relapsing-remitting multiple sclerosis.
TA254 (2012) Fingolimod (Gilenya, Novartis)[339]	21 in total: • 10 EDSS RRMS • 10 EDSS SPMS • Death	• RRMS EQ-5D EDSS 0-9, • SPMS Utility decrement • Caregiver disutilities • Relapse HS disutilities • AE utility decrements • Drug acquisition, administration and monitoring costs • HS Costs EDSS 0-9, • AE Costs	**Uncertainty in the analysis on the population of interest -** analysis of population 1b that excluded people who also met the criteria for population 2 (that is, a population in which people with rapidly evolving severe disease were excluded) was provided. The Committee noted that this analysis generated lower ICERs than those for the whole of population 1b, but was aware of reservations expressed by the manufacturer and the EAG about the small samples on which the subgroup analysis was based **Uncertainty around the improvements in quality of life** - There weren't statistically significant changes from baseline for EQ-5D measures observed for people with relapsing–remitting multiple sclerosis treated with fingolimod or placebo in the	The Committee acknowledged that there was variation in current practice and therefore concluded that fingolimod should be compared with a weighted average of the comparators used in UK clinical practice of RRMS. That the most plausible ICER for fingolimod compared with the weighted average of the comparators was likely to be in the range of £25,000 to £35,000 per QALY gained from the main analysis on population 1b. In supplementary analyses For population 1b, excluding those who also met the criteria for population 2, the EAG concluded that the incremental analysis shows that in both populations Avonex is either dominated or extendedly dominated. The EAG therefore advised

TA, year	Health states	Utilities & Costs	EAG key Criticism	Results
			FREEDOMS trial. A slight, non-statistically significant improvement in the PRIMUS-QoL scale was observed for people treated with fingolimod or Avonex in the TRANSFORMS trial. **Loss of treatment effectiveness** – The Committee preferred a 50% waning of treatment effect after 5 years be included in the base-case analysis. **Unrealistic disability progression** – The Committee noted the concerns of the clinical specialists that the model may not reflect the natural history of multiple sclerosis, because it does not allow for improvement in EDSS scores. **Call for an economic model that reflects clinical practice in UK** - The Committee emphasised that it is important that a new model for multiple sclerosis is developed for any future appraisals of treatments for multiple sclerosis. The new model should ideally be based on UK patient cohorts, should use the best available evidence (including experience to date from the risk-sharing scheme) and should include all currently available treatments for multiple sclerosis, so that future appraisals of treatments for multiple sclerosis are directly relevant to UK clinical practice.	that the cost effectiveness of fingolimod should be derived from incremental analysis.
TA127 (2007) (Tysabri, Biogen Inc.)[34]	21 in total: • 10 EDSS RRMS	• RRMS EQ-5D EDSS 0-9, • SPMS Utility decrement	**Uncertainty in the analysis on the population of interest -** The EAG was critical that the data for the comparators derived from people with RRMS rather than HA RRMS . The company excluded the SENTINEL	The Committee noted that the base case ICERs estimated by the manufacturer for the suboptimal therapy group were £43,400 per QALY gained or higher. It therefore concluded that natalizumab

TA, year	Health states	Utilities & Costs	EAG key Criticism	Results
	• 10 EDSS SPMS • Death	• Caregiver disutilities • Relapse HS disutilities • AE utility decrements • Drug acquisition, administration and monitoring costs • HS Costs EDSS 0-9, • AE Costs	trial SOT RRMS subgroup data from the model, especially that these was relied on for the marketing authorisation. **Loss of treatment effectiveness** – The EAG expressed concern about the extrapolation of 2-year data from the AFFIRM study to a 20-year time horizon. **Unrealistic disability progression** – the EAG expressed concern that, although the transition probabilities in the manufacturer's model were based on data from AFFIRM, the model appeared to predict a higher rate of sustained disability progression at 2 years than reported in AFFIRM. **Treatment effects on progression from RRMS to SPMS** – There wasn't evidence to support the assumption that Natalizumab reduces progression from RRMS to SPMS	would not be a cost-effective use of NHS resources in this group of people. The Committee concluded that the ICER of £32,000 per QALY for natalizumab compared with beta interferon presented by the manufacturer was more likely to be an overestimate. They concluded natalizumab for the treatment of RES RRMS patients was a cost-effective use of NHS resources.

Abbreviations: **AE:** Adverse Events, **ARR:** Annualised Relapse Rate, **CDP**: Confirmed Disability Progression, EAG: External Assessment Group; **EDSS:** Expanded Disability Scale Status, **EQ-5D**: EuroQol five dimensions quality of life index, **GBP £:** Great Britain Pound, **HA RRMS:** Highly Active Relapse Remitting Multiple Sclerosis, **HDA RRMS:** High Disease Activity Relapse Remitting Multiple Sclerosis, **HS:** Health State, **ICER:** Incremental Cost-Effectiveness Ratio, **NHS:** National Health Service, **NMA:** Network Meta-Analysis, **QALY**: Quality Adjusted Life, **RES RRMS:** Rapidly Evolving Severe Relapse Remitting Multiple Sclerosis, **RRMS:** Relapse Remitting Multiple Sclerosis, **SAD**: Sustained Accumulation of Disability, **SOT RRMS:** Sub-Optimally Treated Relapse Remitting Multiple Sclerosis, **SPMS:** Secondary Progressive Multiple Sclerosis,

Appendix 7
Additional MS Registry results

Sample sizes for events in the MS registry are summarized in the tables Table 93 (those that depend on treatment) and Table 94 (those that do not depend on treatment). The sample sizes for those that do not depend on treatment were considerably lower than for those that did depend on treatment, indicating that modelling their treatment dependence would result in poorly informed models.

Table 93 Samples sizes for events in the MS registry that were modelled to depend on treatment

Group	N	.Alemtuzumab	N.Beta.Interferon	N.Cladribine	N.Fingolimod	N.Glatiramer.Acetate	N.Natalizumab	N.Ocrelizumab	N.Ofatumumab	N.Ponesimod	N.Female
Time to EDSS Increase (RRMS Highly Active)	224	12	9	23	65	20	23	43	25	4	186
Time to EDSS Increase (All RRMS)	1016	41	168	35	158	158	177	203	69	7	838
Time to Relapse (RRMS Highly Active)	50	1	11	1	13	11	7	4	1	1	40
Time to Relapse (All RRMS)	191	9	56	2	34	44	28	15	2	1	150

Table 94 Samples sizes for events in the MS registry that were not modelled to depend on treatment

Group	N	N.Alemtuzumab	N.Beta.Interferon	N.Cladribine	N.Fingolimod	N.Glatiramer.Acetate	N.Natalizumab	N.Ocrelizumab	N.Ofatumumab	N.Ponesimod	N.Female
Time to EDSS Decrease (All RRMS)	793	29	159	12	93	138	156	160	43	3	652
Time to EDSS Increase (SPMS)	181	4	69	7	31	21	29	16	4	0	133
Time to Relapse (SPMS)	164	2	79	1	31	28	19	4	0	0	121
Time to SP Conversion (RRMS Highly Active)	66	2	23	0	20	14	3	4	0	0	46
Time to SP Conversion (All RRMS)	222	3	107	2	37	40	29	4	0	0	164

The covariance matrices for the coefficients (on log scale) of the exponential survival models estimated by the MS registry are reported below. These covariances were used when sampling the log rates used for the economic model, although only the coefficient for natalizumab was used from the DMT dependent models.

Table 95 Covariance matrix for coefficients of exponential survival model for Time to EDSS Increase (RRMS Highly Active)

	rate	EDSS	Alemtuzumab	Cladribine	Fingolimod	Glatiramer Acetate	Natalizumab	Ocrelizumab	Ofatumumab	Ponesimod
rate	0.26316339	-0.0188753	-0.2004151	-0.2160293	-0.2131976	-0.2207916	-0.2001307	-0.2067891	-0.1979965	-0.2045135
EDSS	-0.0188753	0.00564056	0.00012407	0.00479009	0.0039439	0.00621322	3.9063E-05	0.00202883	-0.0005987	0.00134879
Alemtuzumab	-0.2004151	0.00012407	0.34285982	0.20010533	0.20008672	0.20013663	0.20000083	0.20004459	0.1999868	0.20002964
Cladribine	-0.2160293	0.00479009	0.20010533	1.20406765	0.20334921	0.20527638	0.20003314	0.20172289	0.19949154	0.20114539
Fingolimod	-0.2131976	0.0039439	0.20008672	0.20334921	0.34561467	0.20434427	0.20002728	0.20141853	0.19958135	0.20094304
Glatiramer Acetate	-0.2207916	0.00621322	0.20013663	0.20527638	0.20434427	0.37351063	0.200043	0.20223477	0.19934048	0.20148569
Natalizumab	-0.2001307	3.9063E-05	0.20000083	0.20003314	0.20002728	0.200043	0.40000021	0.20001402	0.19999582	0.20000931
Ocrelizumab	-0.2067891	0.00202883	0.20004459	0.20172289	0.20141853	0.20223477	0.20001402	0.28406303	0.19978462	0.20048511
Ofatumumab	-0.1979965	-0.0005987	0.1999868	0.19949154	0.19958135	0.19934048	0.19999582	0.19978462	0.53339679	0.1998568
Ponesimod	-0.2045135	0.00134879	0.20002964	0.20114539	0.20094304	0.20148569	0.20000931	0.20048511	0.1998568	1.20032233

Table 96 Covariance matrix for coefficients of exponential survival model for Time to EDSS Increase (All RRMS)

	rate	EDSS	Alemtuzumab	Cladribine	Fingolimod	Glatiramer Acetate	Natalizumab	Ocrelizumab	Ofatumumab	Ponesimod
rate	0.0379168	-0.0042253	-0.0256477	-0.0264687	-0.0245772	-0.0253309	-0.0225739	-0.0250133	-0.024759	-0.0238234
EDSS	-0.0042253	0.00153897	-0.0002433	5.5707E-05	-0.0006332	-0.0003587	-0.0013629	-0.0004744	-0.000567	-0.0009078
Alemtuzumab	-0.0256477	-0.0002433	0.13746535	0.02630698	0.02641591	0.0263725	0.02653128	0.02639079	0.02640544	0.02645932
Cladribine	-0.0264687	5.5707E-05	0.02630698	0.35965108	0.02629286	0.0263028	0.02626645	0.02629861	0.02629526	0.02628292
Fingolimod	-0.0245772	-0.0006332	0.02641591	0.02629286	0.07005459	0.02646338	0.02687657	0.02651098	0.02654909	0.02668931
Glatiramer Acetate	-0.0253309	-0.0003587	0.0263725	0.0263028	0.02646338	0.06639939	0.02663346	0.02642636	0.02644795	0.02652738
Natalizumab	-0.0225739	-0.0013629	0.02653128	0.02626645	0.02687657	0.02663346	0.05191298	0.0267359	0.02681792	0.02711971
Ocrelizumab	-0.0250133	-0.0004744	0.02639079	0.02629861	0.02651098	0.02642636	0.0267359	0.04820114	0.02649057	0.02659561
Ofatumumab	-0.024759	-0.000567	0.02640544	0.02629526	0.02654909	0.02644795	0.02681792	0.02649057	0.12652468	0.02665025
Ponesimod	-0.0238234	-0.0009078	0.02645932	0.02628292	0.02668931	0.02652738	0.02711971	0.02659561	0.02665025	1.0268511

Table 97 Covariance matrix for coefficients of exponential survival model for Time to Relapse (RRMS Highly Active)

	rate	EDSS	Alemtuzumab	Cladribine	Fingolimod	Glatiramer Acetate	Natalizumab	Ocrelizumab	Ofatumumab	Ponesimod
rate	0.1760278	-0.0212619	-0.09098	-0.112242	-0.1078575	-0.1035607	-0.0569426	-0.0976834	-0.112242	-0.133504
EDSS	-0.0212619	0.00885927	-0.0141752	-0.0053159	-0.0071428	-0.0089332	-0.0283577	-0.0113821	-0.0053159	0.00354338
Alemtuzumab	-0.09098	-0.0141752	1.14768071	0.13350564	0.13642877	0.13929343	0.17037343	0.14321177	0.13350564	0.11933043
Cladribine	-0.112242	-0.0053159	0.13350564	1.12818956	0.12928594	0.13036023	0.14201567	0.13182966	0.12818972	0.12287382
Fingolimod	-0.1078575	-0.0071428	0.13642877	0.12928594	0.20768195	0.13220238	0.14786343	0.13417681	0.12928594	0.12214312
Glatiramer Acetate	-0.1035607	-0.0089332	0.13929343	0.13036023	0.13220238	0.24511877	0.15359423	0.13647701	0.13036023	0.12142704
Natalizumab	-0.0569426	-0.0283577	0.17037343	0.14201567	0.14786343	0.15359423	0.35862733	0.16143293	0.14201567	0.11365796
Ocrelizumab	-0.0976834	-0.0113821	0.14321177	0.13182966	0.13417681	0.13647701	0.16143293	0.38962324	0.13182966	0.12044757
Ofatumumab	-0.112242	-0.0053159	0.13350564	0.12818972	0.12928594	0.13036023	0.14201567	0.13182966	1.12818956	0.12287382
Ponesimod	-0.133504	0.00354338	0.11933043	0.12287382	0.12214312	0.12142704	0.11365796	0.12044757	0.12287382	1.12641703

Table 98 Covariance matrix for coefficients of exponential survival model for Time to Relapse (All RRMS)

	rate	EDSS	Alemtuzumab	Cladribine	Fingolimod	Glatiramer Acetate	Natalizumab	Ocrelizumab	Ofatumumab	Ponesimod
rate	0.0531041	-0.0074094	-0.0248499	-0.0294932	-0.0219009	-0.0251326	-0.0169087	-0.0198371	-0.0335028	-0.0382852
EDSS	-0.0074094	0.00191196	0.0001186	0.0013168	-0.0006423	0.00019157	-0.0019306	-0.0011749	0.00235144	0.00358552
Alemtuzumab	-0.0248499	0.0001186	0.14939758	0.02447193	0.02435039	0.02440212	0.02427048	0.02431736	0.02453611	0.02461266
Cladribine	-0.0294932	0.0013168	0.02447193	0.52529706	0.02394784	0.02452217	0.02306063	0.02358107	0.02600972	0.02685964
Fingolimod	-0.0219009	-0.0006423	0.02435039	0.02394784	0.05686411	0.02432588	0.02503884	0.02478496	0.02360024	0.02318564
Glatiramer Acetate	-0.0251326	0.00019157	0.02440212	0.02452217	0.02432588	0.04940943	0.02419681	0.02427252	0.02462584	0.02474949
Natalizumab	-0.0169087	-0.0019306	0.02427048	0.02306063	0.02503884	0.02419681	0.06480111	0.02557657	0.02201592	0.02076985

Ocrelizumab	-0.0198371	-0.0011749	0.02431736	0.02358107	0.02478496	0.02427252	0.02557657	0.10844554	0.02294528	0.02218694
Ofatumumab	-0.0335028	0.00235144	0.02453611	0.02600972	0.02360024	0.02462584	0.02201592	0.02294528	0.52728212	0.02879993
Ponesimod	-0.0382852	0.00358552	0.02461266	0.02685964	0.02318564	0.02474949	0.02076985	0.02218694	0.02879993	1.03111405

Table 99 Covariance matrix for coefficients of exponential survival model for Time to EDSS Decrease (All RRMS)

	rate	EDSS
rate	0.048537	-0.0099457
EDSS	-0.0099457	0.00242531

Table 100 Covariance matrix for coefficients of exponential survival model for Time to EDSS Increase (SPMS)

	rate	**EDSS**
rate	0.41327905	-0.0685228
EDSS	-0.0685228	0.01220504

Table 101 Covariance matrix for coefficients of exponential survival model for Time to Relapse (SPMS)

	rate	**EDSS**
rate	0.86895777	-0.1357356
EDSS	-0.1357356	0.02188323

Table 102 Covariance matrix for coefficients of exponential survival model for Time to SP Conversion (RRMS Highly Active)

	rate	**EDSS**
rate	0.45009625	-0.0734639
EDSS	-0.0734639	0.01242186

Table 103 Covariance matrix for coefficients of exponential survival model for Time to SP Conversion (All RRMS)

	rate	**EDSS**
rate	0.13046351	-0.0207383
EDSS	-0.0207383	0.0034233

The results of fitting the multistate model to the All RRMS population are provided in Table 104 with standard errors in Table 105.

Table 104 MS registry log rates of transition between EDSS states based on multistate model

	0	1	2	3	4	5	6	7	8
0	0	5.33192944	0	0	0	0	0	0	0
1	6.21287963	0	2.06546476	0	0	0	0	0	0
2	0	-0.714375	0	3.94007716	0	0	0	0	0
3	0	0	3.89699664	0	-0.3884832	0	0	0	0
4	0	0	0	-0.3449541	0	0.16070213	0	0	0
5	0	0	0	0	0.59315005	0	0.31408698	0	0
6	0	0	0	0	0	-1.191966	0	-1.9983354	0
7	0	0	0	0	0	0	-1.1958821	0	-1.4518141
8	0	0	0	0	0	0	0	1.25944346	0

Table 105 Standard errors for MS registry log rates of transition between EDSS states based on multistate model

	0	1	2	3	4	5	6	7	8
0	0	2.10122434	0	0	0	0	0	0	0
1	2.08691526	0	0.345469	0	0	0	0	0	0
2	0	0.30187187	0	1.61466577	0	0	0	0	0
3	0	0	1.61681602	0	0.1488902	0	0	0	0
4	0	0	0	0.16046662	0	0.17763808	0	0	0
5	0	0	0	0	0.19043778	0	0.16388654	0	0
6	0	0	0	0	0	0.15350255	0	0.16672652	0
7	0	0	0	0	0	0	0.20999212	0	0.70836177
8	0	0	0	0	0	0	0	0.78283474	0

Appendix 8
Additional economic results

The total costs, total QALYs, and net benefits from the sensitivity analyses are presented below.

Table 106 Costs, QALYs and Net Benefit for treatments in comparison to Natalizumab IV (publicly available list prices) for Scenario 1 (All RRMS MS Registry population)

Treatment	Total costs (95% CrI)	Total QALYs (95% CrI)	Net benefit at £20,000/QALY (95% CrI)	Net benefit at £30,000/QALY (95% CrI)
Natalizumab-IV	598795.89 (541344.80, 668003.78)	9.39 (7.23, 12.17)	-410973.22 (-507725.34, -328395.74)	-317061.89 (-435024.42, -208253.29)
Natalizumab-SC	598390.47 (548051.13, 675501.89)	9.40 (7.12, 11.93)	-410458.67 (-512092.84, -336732.27)	-316492.77 (-434697.06, -225168.41)
Natalizumab biosimilar-IV	579908.89 (523045.16, 652685.77)	9.48 (7.08, 12.23)	-390247.57 (-495770.40, -309160.37)	-295416.90 (-415763.27, -201317.59)
Natalizumab biosimilar-SC	582183.63 (529485.06, 660590.52)	9.44 (7.34, 12.33)	-393354.55 (-488369.63, -317375.00)	-298940.01 (-405165.50, -204396.00)
Fingolimod	554644.56 (506013.91, 605241.50)	9.07 (6.74, 11.89)	-373332.15 (-439292.78, -293001.89)	-282675.94 (-366349.33, -174048.65)
Alemtuzumab	392265.32 (339307.14, 442588.68)	9.58 (7.28, 12.22)	-200663.61 (-279920.30, -126785.15)	-104862.75 (-200969.95, -11332.86)
Cladribine	388725.14 (342211.85, 436994.17)	8.76 (6.27, 11.39)	-213531.13 (-291153.75, -150969.01)	-125934.13 (-225773.91, -42879.73)
Ponesimod	482553.79 (439545.43, 555432.90)	8.95 (6.61, 11.37)	-303468.40 (-398720.43, -221229.76)	-213925.71 (-326068.53, -112605.33)
Ofatumumab	581498.65 (524699.05, 673961.13)	9.48 (7.18, 11.71)	-391816.87 (-516957.99, -301301.26)	-296975.98 (-438103.52, -191451.79)
Ocrelizumab	610973.28 (550077.19, 688108.24)	9.48 (7.22, 12.12)	-421311.97 (-517712.16, -341047.50)	-326481.32 (-435151.70, -224920.07)
Peginterferon-beta-1 SC 125µg	378806.29 (333919.20, 440357.27)	9.29 (7.04, 11.77)	-192936.46 (-267297.66, -127636.15)	-100001.55 (-196554.26, -14198.13)
Interferon-beta-1a SC 22µg	397488.66 (350587.74, 453451.67)	9.23 (6.98, 11.82)	-212813.70 (-284706.94, -139697.08)	-120476.22 (-215635.75, -24732.19)
Interferon-beta-1a SC 44µg	378381.40 (329630.26, 424331.74)	9.05 (6.15, 11.75)	-197470.92 (-280882.90, -132525.87)	-107015.68 (-215978.35, -29124.46)

Treatment	Total costs (95% CrI)	Total QALYs (95% CrI)	Net benefit at £20,000/QALY (95% CrI)	Net benefit at £30,000/QALY (95% CrI)
Interferon-beta-1a IM 30µg	387836.50 (339638.11, 448683.70)	8.82 (5.92, 11.53)	-211489.18 (-294277.50, -132080.67)	-123315.52 (-232329.70, -17747.86)
Interferon-beta-1b SC 250µg	377187.75 (326714.14, 428150.07)	8.83 (6.48, 11.68)	-200597.82 (-281996.00, -127701.81)	-112302.86 (-215219.01, -16976.85)
Glatiramer Acetate 20mg	368533.08 (318421.90, 424950.62)	9.04 (6.67, 11.99)	-187774.06 (-269458.79, -120769.00)	-97394.54 (-191000.77, -11625.21)
Glatiramer Acetate 40mg	367001.59 (323298.80, 423995.21)	9.00 (6.79, 11.74)	-187043.11 (-261447.24, -121999.46)	-97063.88 (-189595.24, -10080.72)

Table 107 Costs, QALYs and Net Benefit for treatments in comparison to Natalizumab IV (publicly available list prices) for Scenario 2 (base-case w/ random effects NMA)

Treatment	Total costs (95% CrI)	Total QALYs (95% CrI)	Net benefit at £20,000/QALY (95% CrI)	Net benefit at £30,000/QALY (95% CrI)
Natalizumab-IV	598372.81 (546324.59, 673317.57)	9.58 (7.19, 12.63)	-406861.30 (-503937.23, -332801.32)	-311105.55 (-422956.65, -210429.32)
Natalizumab-SC	594613.77 (544928.33, 667468.89)	9.65 (7.29, 12.75)	-401652.27 (-490794.21, -335379.62)	-305171.52 (-415156.58, -206711.84)
Natalizumab biosimilar-IV	578589.43 (516709.91, 650346.20)	9.56 (7.17, 12.94)	-387487.40 (-484230.09, -302809.47)	-291936.39 (-413491.22, -173319.17)
Natalizumab biosimilar-SC	577461.75 (519695.59, 650792.03)	9.59 (7.05, 12.70)	-385640.28 (-491843.00, -301175.40)	-289729.55 (-413548.83, -185442.23)
Fingolimod	548613.06 (512651.42, 614318.67)	9.37 (6.83, 12.23)	-361304.77 (-435943.23, -301588.96)	-267650.63 (-350307.96, -190427.15)
Alemtuzumab	395735.19 (349536.35, 463348.50)	9.79 (7.02, 13.10)	-199964.30 (-291544.28, -106482.27)	-102078.85 (-208802.63, 13607.02)
Cladribine	388510.58 (342885.39, 443015.67)	8.91 (6.14, 11.54)	-210374.01 (-293864.41, -137535.89)	-121305.73 (-232011.97, -34532.84)
Ponesimod	480555.51 (427234.29, 547633.22)	9.10 (6.27, 11.50)	-298589.89 (-406677.15, -218011.39)	-207607.07 (-344500.87, -106979.46)
Ofatumumab	583003.39 (528763.35, 657647.34)	9.41 (6.84, 12.76)	-394781.13 (-494840.15, -307948.05)	-300670.01 (-415571.15, -188608.84)
Ocrelizumab	608513.00 (561119.72, 669324.12)	9.66 (7.61, 12.40)	-415333.26 (-497062.28, -347017.17)	-318743.39 (-411116.00, -229319.80)
Peginterferon-beta-1 SC 125µg	376669.86 (326404.56, 445471.06)	9.52 (7.25, 12.34)	-186209.50 (-271379.16, -104614.15)	-90979.31 (-200229.96, 19391.44)

Treatment	Total costs (95% CrI)	Total QALYs (95% CrI)	Net benefit at £20,000/QALY (95% CrI)	Net benefit at £30,000/QALY (95% CrI)
Interferon-beta-1a SC 22µg	398806.56 (346242.70, 457440.61)	9.35 (7.09, 12.51)	-211717.04 (-309743.62, -126530.35)	-118172.29 (-237616.66, -5062.01)
Interferon-beta-1a SC 44µg	374019.28 (322168.34, 426849.54)	9.35 (6.85, 12.41)	-186928.25 (-276500.32, -107158.27)	-93382.73 (-200596.19, 12988.73)
Interferon-beta-1a IM 30µg	386799.83 (338733.28, 445194.14)	8.97 (6.29, 12.07)	-207340.72 (-298670.32, -127009.53)	-117611.17 (-230676.28, -10687.99)
Interferon-beta-1b SC 250µg	364990.86 (313505.86, 430970.20)	9.29 (6.59, 12.66)	-179248.16 (-284117.16, -76551.06)	-86376.81 (-219162.58, 44489.20)
Glatiramer Acetate 20mg	362912.60 (306509.82, 416675.82)	9.11 (6.60, 12.28)	-180623.98 (-267384.96, -94989.34)	-89479.67 (-200441.97, 11212.71)
Glatiramer Acetate 40mg	367784.97 (318208.39, 432781.53)	9.11 (6.36, 12.11)	-185545.43 (-266212.66, -101760.69)	-94425.67 (-205747.54, 9151.66)

Table 108 Costs, QALYs and Net Benefit for treatments in comparison to Natalizumab IV (publicly available list prices) for Scenario 3 (base-case & assuming JCV testing provided free of charge by manufacturers)

Treatment	Total costs (95% CrI)	Total QALYs (95% CrI)	Net benefit at £20,000/QALY (95% CrI)	Net benefit at £30,000/QALY (95% CrI)
Natalizumab-IV	562443.81 (511510.68, 641789.27)	11.18 (8.22, 14.43)	-338935.69 (-473880.31, -251626.66)	-227181.64 (-388596.81, -112286.13)
Natalizumab-SC	562682.85 (511613.14, 654456.97)	11.20 (8.23, 14.73)	-338667.64 (-471536.84, -261249.30)	-226660.03 (-384668.83, -118997.45)
Natalizumab biosimilar-IV	544207.05 (498616.93, 626417.06)	11.14 (8.20, 14.49)	-321369.48 (-437442.09, -242310.50)	-209950.69 (-358348.65, -98012.69)
Natalizumab biosimilar-SC	541662.28 (488163.66, 618771.01)	11.16 (8.18, 14.55)	-318498.59 (-446802.32, -235714.80)	-206916.75 (-362445.55, -89314.51)
Fingolimod	515561.88 (465834.49, 592723.88)	10.90 (7.84, 14.58)	-297463.95 (-431552.97, -211288.35)	-188414.98 (-357264.51, -77028.43)
Alemtuzumab	360937.84 (314526.46, 415502.63)	11.32 (8.49, 14.61)	-134570.29 (-212319.32, -68298.46)	-21386.52 (-125960.31, 73934.23)
Cladribine	348440.03 (304305.36, 414499.40)	10.66 (7.41, 14.59)	-135228.91 (-254511.61, -61569.08)	-28623.35 (-173771.00, 66301.37)
Ponesimod	444057.70 (395803.91, 518072.17)	10.90 (7.24, 14.25)	-226084.60 (-344152.07, -141369.99)	-117098.04 (-273087.09, -4807.75)

Treatment	Total costs (95% CrI)	Total QALYs (95% CrI)	Net benefit at £20,000/QALY (95% CrI)	Net benefit at £30,000/QALY (95% CrI)
Ofatumumab	549680.95 (496084.71, 626940.15)	11.08 (8.02, 14.48)	-328052.89 (-462936.26, -251872.52)	-217238.85 (-380934.32, -116838.53)
Ocrelizumab	576608.50 (525932.16, 658066.04)	11.28 (8.05, 14.57)	-351082.95 (-481370.01, -276591.86)	-238320.18 (-397492.63, -137618.56)
Peginterferon-beta-1 SC 125µg	343178.10 (296942.17, 398482.75)	11.09 (8.13, 14.37)	-121352.36 (-235653.66, -40747.38)	-10439.50 (-154336.51, 95596.30)
Interferon-beta-1a SC 22µg	358910.56 (312218.91, 417588.57)	11.02 (7.92, 14.47)	-138446.88 (-237720.76, -65451.34)	-28215.03 (-153811.30, 69279.58)
Interferon-beta-1a SC 44µg	341087.60 (298992.52, 413554.46)	10.85 (8.16, 14.29)	-124118.66 (-224930.42, -38395.37)	-15634.19 (-141681.51, 101602.13)
Interferon-beta-1a IM 30µg	348343.06 (296631.36, 414106.34)	10.73 (7.07, 14.23)	-133825.37 (-266131.81, -49270.63)	-26566.52 (-189372.65, 83927.33)
Interferon-beta-1b SC 250µg	336548.87 (291412.61, 413549.07)	10.78 (7.29, 14.16)	-121033.61 (-249343.45, -35322.27)	-13275.99 (-181840.36, 96667.75)
Glatiramer Acetate 20mg	328795.83 (288931.79, 394107.22)	10.91 (7.44, 14.37)	-110671.59 (-232424.76, -34809.97)	-1609.46 (-155847.98, 99754.61)
Glatiramer Acetate 40mg	328710.26 (279774.89, 393415.70)	10.88 (7.53, 14.23)	-111206.41 (-233044.31, -25103.97)	-2454.49 (-160987.35, 114599.29)

Table 109 Costs, QALYs and Net Benefit for treatments in comparison to Natalizumab IV (publicly available list prices) for Scenario 4 (base-case & assuming lowest generic prices)

Treatment	Total costs (95% CrI)	Total QALYs (95% CrI)	Net benefit at £20,000/QALY (95% CrI)	Net benefit at £30,000/QALY (95% CrI)
Natalizumab-IV	567206.62 (515989.58, 646969.91)	11.18 (8.22, 14.43)	-343698.51 (-478923.66, -256427.65)	-231944.45 (-393640.16, -116759.62)
Natalizumab-SC	567460.49 (515964.10, 659385.70)	11.20 (8.23, 14.73)	-343445.28 (-476538.97, -266378.65)	-231437.68 (-389729.42, -123532.80)
Natalizumab biosimilar-IV	548995.60 (503066.35, 631754.31)	11.14 (8.20, 14.49)	-326158.04 (-442264.89, -247021.95)	-214739.25 (-363107.98, -102724.15)
Natalizumab biosimilar-SC	546412.78 (492243.98, 623904.43)	11.16 (8.18, 14.55)	-323249.09 (-451680.81, -240479.30)	-211667.25 (-367304.79, -94079.01)
Fingolimod	335804.52 (290819.35, 393084.47)	10.90 (7.84, 14.58)	-117706.59 (-223030.88, -36799.35)	-8657.63 (-139474.60, 101895.35)

Treatment	Total costs (95% CrI)	Total QALYs (95% CrI)	Net benefit at £20,000/QALY (95% CrI)	Net benefit at £30,000/QALY (95% CrI)
Alemtuzumab	362426.34 (315802.47, 417204.72)	11.32 (8.49, 14.61)	-136058.79 (-213370.79, -69826.47)	-22875.02 (-127011.78, 72508.05)
Cladribine	349930.51 (305487.25, 415856.20)	10.66 (7.41, 14.59)	-136719.39 (-255990.66, -62870.99)	-30113.83 (-175250.05, 64626.55)
Ponesimod	445558.21 (397147.44, 519340.02)	10.90 (7.24, 14.25)	-227585.10 (-345288.63, -142929.03)	-118598.55 (-274455.67, -6467.86)
Ofatumumab	551178.38 (497587.54, 628450.25)	11.08 (8.02, 14.48)	-329550.31 (-464446.36, -253257.69)	-218736.28 (-382444.42, -118410.09)
Ocrelizumab	578096.88 (527458.10, 659330.20)	11.28 (8.05, 14.57)	-352571.33 (-482590.32, -277846.93)	-239808.56 (-398649.45, -139338.35)
Peginterferon-beta-1 SC 125µg	344691.51 (298364.16, 399694.49)	11.09 (8.13, 14.37)	-122865.78 (-236905.31, -42009.03)	-11952.91 (-155588.17, 94057.25)
Interferon-beta-1a SC 22µg	360394.11 (313452.66, 419105.16)	11.02 (7.92, 14.47)	-139930.42 (-239309.88, -66790.88)	-29698.58 (-155045.02, 67744.35)
Interferon-beta-1a SC 44µg	342581.14 (300199.52, 415208.40)	10.85 (8.16, 14.29)	-125612.20 (-226249.01, -39863.25)	-17127.73 (-143208.54, 100029.18)
Interferon-beta-1a IM 30µg	349838.95 (297790.59, 415484.27)	10.73 (7.07, 14.23)	-135321.26 (-267410.99, -50722.21)	-28062.41 (-190651.83, 82461.43)
Interferon-beta-1b SC 250µg	338035.98 (292809.83, 414894.48)	10.78 (7.29, 14.16)	-122520.73 (-250728.60, -36668.90)	-14763.10 (-183228.83, 95326.42)
Glatiramer Acetate 20mg	324077.33 (283831.26, 388513.07)	10.91 (7.44, 14.37)	-105953.08 (-227710.21, -30270.14)	3109.04 (-149580.17, 104585.66)
Glatiramer Acetate 40mg	324036.70 (274440.80, 388793.61)	10.88 (7.53, 14.23)	-106532.85 (-226977.80, -20437.00)	2219.07 (-154920.84, 119387.08)

Natalizumab and Tyruko (natalizumab biosimilar) for treating highly active relapsing-remitting multiple sclerosis after at least one disease modifying therapy: a systematic review and economic model

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Keywords

Multiple Sclerosis; Systematic Reviews; Network Meta-analysis; Economic model

Abstract

Background

Multiple sclerosis (MS) is an immune-mediated inflammatory disease, causing long-term disability in young adults. Most cases begin as relapsing-remitting MS (RRMS). Some people have a form of RRMS known as highly active RRMS (HARRMS), defined as MS with unchanged or increased disease activity despite prior treatment with at least one disease-modifying therapy (DMT).

Objectives

To appraise the clinical and cost effectiveness of natalizumab (Tysabri) and natalizumab biosimilar (Tyruko) for treating HARRMS compared to other DMT.

Design

Systematic review with network meta-analysis (NMA) and economic model.

Results

We included 42 studies (22, 409 participants): 40 in people with RRMS and two in HARRMS. Six studies also reported data separately for HARRMS. Only four studies evaluated natalizumab or natalizumab biosimilar; none provided data on those with HARRMS. Follow-up ranged from 4 to 36 (median 24) months.

Most interventions reduced relapses (39 studies, 17 interventions) and MRI lesions (19 studies, 11 interventions for Gd+ lesions and 17 studies, 12 interventions for T2 weighted lesions) compared to placebo. Alemtuzumab, ocrelizumab, cladribine, natalizumab, fingolimod and peginterferon beta 1a reduced disease progression compared to placebo (15 studies, 12 interventions). There were no differences in any adverse events (AEs) (24 studies, 16 interventions), serious AEs (31 studies, 15 interventions) or treatment related AEs (8 studies, no NMA) for any intervention compared to placebo. Fingolimod, glatiramer acetate, interferon beta 1a, interferon beta 1b and peginterferon beta 1a were associated with an increased treatment discontinuation (29 studies, 13 interventions). There was little evidence for a difference in quality of life. There was no evidence of a difference between natalizumab and natalizumab biosimilar for relapse rates (RR 0.65 (95% credible interval (CrI) 0.33, 1.23), Gd+ lesions (HR 1.29 (0.69, 2.37), T2 weighted lesions (HR 1.07 (0.73, 1.57)), any AEs (HR 1.06 (0.77, 1.46) or treatment discontinuation (HR 0.48 (0.13, 1.76)).

Data in HARRMS were available for fingolimod, ocrelizumab, alemtuzumab, cladribine, beta-interferon, AHSCT, and placebo. We also included one study on natalizumab conducted in a population that was close to our definition of HARRMS. All interventions except interferon beta 1a were associated with reduced relapse risk compared to placebo (6 studies; 7 interventions).

Compared with natalizumab-IV, natalizumab biosimilar-IV and natalizumab-SC, all treatments had greater net benefit at £20-30,000/QALY, with the only exception being ocrelizumab which had lower net benefits. Costs were generally higher on natalizumab than other treatments, though there was no difference in QALYs with 95% CrI completely

overlapping. The results and conclusions were unchanged under all sensitivities. Value of information analysis found that the greatest contributor to decision uncertainty was the effectiveness of treatments.

Conclusions

There is no direct evidence on the effectiveness of natalizumab or its biosimilar in patients with HARRMS. Limited data suggest similar effectiveness in patients with RRMS. The economic model found that natalizumab and natalizumab biosimilar were not cost-effective compared to any of the included comparators in HARRMS, with the only exception being ocrelizumab.

Future work

There is need for studies of natalizumab and natalizumab biosimilar in people with HARRMS.

Study registration

The review was registered at PROSPERO (CRD42024556838).

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List of Abbreviations

Term	Definition
AE	Adverse Event
AHSCT	Autologous Haematopoietic Stem Cell Treatment
AI	Artificial Intelligence
APDDS	Adapted Patient Determined Disease Steps
ARR	Annualised Relapse Rate
AV	Atrioventricular
BCEA	Bayesian Cost-Effectiveness Analysis
BGR	Brookes-Gelman-Rubin
BNF	British National Formulary
CBA	Cost-Benefit Analysis
CC	Complication and Comorbidity
CDP	Confirmed Disease Progression
CE	Cost-Effectiveness
CEA	Cost-Effectiveness Analysis
CEAC	Cost-Effectiveness Acceptability Curve
CEAF	Cost-Effectiveness Acceptability Frontier
CI	Confidence interval
CMA	Cost-Minimisation Analysis
CNS	Central Nervous System
CRD	Centre for Reviews and Dissemination
CrI	Credible Interval
CSF	Cerebrospinal Fluid
CUA	Cost-Utility Analysis
DCP	Disease Control Priorities
DES	Discrete Event Simulation
DESCEM	Discrete Event Simulation for Cost-Effectiveness Modeling
DIC	Deviance Information Criterion
DMD	Disease-Modifying Drug
DMT	Disease-Modifying Therapy
DP	Determiner Phrase
DSU	Decision Support Unit
EAG	External Assessment Group
EED	Economics Evaluations Database
EDSS	Expanded Disability Scale Status
EQ-5D	EuroQol 5 dimensions quality of life index
EBV	Epstein-Barr virus
EVPPI	Expected Value of Partial Perfect Information
FDA	Federal Drugs Agency
GP	Gaussian processes
GAM	Generalised Additive Models
GBP	Great Britain Pound
GBT	Generative Pre-Trained Transformer
HADS	Hospital Anxiety and Depression Scale
HARRMS	Highly active relapsing remitting multiple sclerosis
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HLA	Human Leukocyte Antigen

Term	Definition
HPV	Human Papillomavirus
HR	Hazard Ratio
HRG	Healthcare Resource Group
HRQoL	Health Related Quality of Life
HS	Health State
HTA	Health Technology Assessment
ICER	Incremental Cost-Effectiveness Ratio
ICTRP	International Clinical Trials Registry Platform
IFNB	Interferon beta
IQR	Interquartile range
ISPOR	International Society for Outcomes Research
ITT	Intention to treat
IM	Intramuscular injection
IV	Intravenous
JC	John Cunningham human polyomavirus
LCI	Lower Confidence Interval
MCMC	Markov Chain Monte Carlo
MD	Mean Difference
MLMC	Multilevel Monte Carlo
MPES	Multiparameter evidence synthesis
MRI	Magnetic Resonance Imaging
MS	Multiple Sclerosis
NA	Not Applicable
NCT	National Clinical Trial
NHS	National Health Service
NHS EED	NHS Economic Evaluations Database
NI	No information
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
NMA	Network Meta-Analysis
NR	Not Reported
PCR	Polymerase chain reaction
PICO	Patient, Population or Problem; Intervention; Comparison; Outcome (Cochrane)
PML	Progressive Multifocal Leucoencephalopathy
POCT	Point-Of-Care-Testing
PPMS	Primary Progressive Multiple Sclerosis
QALY	Quality Adjusted Life Year
QoL	Quality of Life
RCT	Randomized Controlled Trial
RES RRMS	Rapidly Evolving Severe Relapse Remitting Multiple Sclerosis
RR	Rate Ratio
RRMS	Relapse Remitting Multiple Sclerosis
SAD	Sustained Accumulation of Disability
SC	Subcutaneous injection
SD	Standard deviation
SE	Standard error
SF-36	Self-Reported-36 quality of life index
SLR	Systematic Literature Review
SMDM	Society for Medical Decision Making

Term	Definition
SOT RRMS	Sub-Optimally Treated Relapse Remitting Multiple Sclerosis
SPMS	Secondary Progressive Multiple Sclerosis
TA	Technology Appraisal
TAG	Technology Assessment Group
TIA	Transient Ischaemic Attack
TSD	Technical Support Document
UCI	Upper confidence interval
UK	United Kingdom
UME	Unrelated Mean Effects
UVB	Ultraviolet B light
VEP	Visually Evoked Potential
VOI	Value-Of-Information
WTP	Willingness-To-Pay
WHO	World Health Organisation

Plain English Summary

What is the problem?

Multiple sclerosis (MS) is a common lifelong condition affecting the brain and spine. It can cause symptoms like vision problems, trouble with balance, movement, thinking, and bladder or bowel control. MS often starts in early adulthood and usually worsens over time, though this varies.

The exact cause of MS is unclear, but factors like genetics, vitamin D levels, inflammation, smoking, and viral infections may increase the risk. Treatments can manage symptoms, slow disease progression, and improve quality of life.

Most people with MS have relapsing-remitting MS (RRMS), marked by relapses—periods when symptoms worsen or new ones appear, lasting weeks or months. Symptoms may improve after a relapse but often leave lasting effects. Some patients, known as having "highly active RRMS (HARRMS)", continue to have relapses despite treatment and may need different medications.

What did we do?

We wanted to know whether a drug called natalizumab (Tysabri) and similar drug known as natalizumab biosimilar (Tyruko) are effective for patients with HARRMS, when compared with other drugs already in use for these patients. We also wanted to know whether using these drugs is a good use of NHS money. We looked at existing research and developed cost models to answer these questions.

What did we find?

No studies were found that specifically evaluated Tysabri or Tyruko in people with HARRMS. However, four studies in people with RRMS showed these drugs seemed equally effective for this group. Evidence from other treatments suggests that drugs effective in general RRMS also work well in HARRMS, so it's reasonable to expect that Tysabri and Tyruko might have similar results for these patients. However, evidence from our cost model suggested that these drugs do not represent good value for money compared to other treatments for MS.

Word count: 294

Scientific Summary

Background

Multiple sclerosis (MS) is a chronic autoimmune condition that affects the central nervous system, usually starting in early adulthood and often causing long-term disability in young adults. Symptoms can vary but commonly include fatigue, muscle weakness, vision problems, and cognitive issues. In the UK, around 130 in every 100,000 people are affected. Most cases (85–90%) begin as relapsing-remitting MS (RRMS), with periods of relapses and remissions, which can later progress to secondary progressive MS (SPMS). A smaller group have primary progressive MS (PPMS) from the start. RRMS can be further categorised based on disease activity. Highly active RRMS (HARRMS), the focus of this appraisal, is broadly defined as MS with unchanged or increased disease activity—clinically or radiologically—despite prior treatment with at least one disease-modifying therapy (DMT). Management typically includes multidisciplinary care and DMTs to reduce relapses and slow progression.

Objectives

The overall aim was to appraise the clinical and cost effectiveness of natalizumab (Tysabri) and natalizumab biosimilar (Tyruko) within their marketing authorisations for treating HARRMS after at least one disease modifying therapy.

Methods

Clinical effectiveness review

We conducted a systematic literature review (SLR) with network meta-analysis (NMA). As we did not expect to find many RCTs in people with HARRMS, we broadened inclusion to people with RRMS. We included RCTs that compared one of the interventions (natalizumab or natalizumab biosimilar) or comparators of interest (glatiramer acetate, interferon beta-1a, interferon beta-1b, peginterferon beta-1a, alemtuzumab, cladribine tablets, fingolimod, ocrelizumab, ofatumumab, ponesimod, and AHSCT) to each other or to placebo.

We searched MEDLINE, EMBASE and trial registries from inception to April 2024. We screened existing relevant technology appraisals, SLRs and submissions from manufacturers of natalizumab and natalizumab biosimilar.

Title and abstract screening and assessment of full text papers were conducted by two reviewers independently. Data extraction and risk of bias assessment were performed by one reviewer and checked by a second. Risk of bias was assessed with the RoB 2 tool at the outcome level. We extracted and synthesized data on the following outcomes:

- Annualised relapse rate (ARR)
- Disability progression confirmed at 3 and 6 months (CDP3 and CDP6)
- MRI measurements (proportion of participants with gadolinium enhancing (Gd+) or new or enlarging T2 lesions)
- Adverse effects (AEs) of treatment (any AEs, treatment related AEs, serious AEs, AEs leading to treatment discontinuation)
- Health-related quality of life assessed using the EQ-5D or SF-36 scales

For each outcome, we provided a narrative summary of study details, risk of bias, and results. Bayesian random and fixed effects NMA was performed to compare the efficacy and

safety of treatment options using the available trial information. Most treatments were not compared in head-to-head RCTs, and NMA allowed for the use of indirect information to make that comparison. We selected the model (random vs fixed effects) that provided the best fit to the data. We presented results as comparisons of each intervention in the network with placebo, mean ranking of each intervention, probability that each intervention would rank first or in specific positions, and a pairwise comparison of each intervention included in the network. Bayesian 95% credible intervals (CrI) were used to represent uncertainty. We used the R package 'multinma' for all analyses.

Cost-effectiveness

We undertook an independent economic assessment using a Discrete Event Simulation (DES) individual patient model. Previous NICE Technology Assessments (TAs) have been criticised as they did not capture treatment sequencing and that they were unable to accurately reflect the course of the condition. Our DES aimed to overcome these limitations by using by modelling of treatment sequences

To design the model, we reviewed models used in previous NICE TAs. These used very similar Markov multistate models based on EDSS severity with transition rates informed by the British Columbia Multiple Sclerosis registry and London Ontario MS databases and treatment effects by individual trials and NMA. Our DES modelled EDSS as an individual attribute, aligning with the structure of the prior models. We also included attributes for age, sex, SPMS status and current treatment. Simulated events were EDSS increase, EDSS decrease, SPMS progression, relapse, SAEs, treatment discontinuation, and death. Patients could switch treatment twice, meaning that up to 4th line therapy was modelled. Patients who progressed SPMS could experience the events EDSS increase, relapse, SAEs, and death.

Event rates were informed by a combination of new analyses conducted by the UK MS Registry and treatment effects of ARR and CDP6 estimated by the NMA. Baseline SAEs and discontinuation came from AFFIRM and ANTELOPE with treatment effects from the NMA. Rates in the SPMS population were informed by the MS Registry analyses as no treatment effects were assumed. Our approach to costs and utilities were aligned with previous TAs. The cost of John Cunningham human polyomavirus (JCV) testing was included for both natalizumab and natalizumab biosimilar as clinical advice was that the manufacturer scheme of paying for JCV testing is not widely available. The economic model was implemented in the R programming language using the DESCEM package and the code was validated by an independent analyst at the consultancy Evidera. The model precited EDSS severity over time was validated by comparison to a Markov model prediction.

The selected base case analysis used the HARRMS population from the MS Registry for baseline rates and the base case selection from the NMA results. Treatment class effects was assumed where relative treatment effects not estimated by NMA. Sensitivity analyses were conducted using the All RRMS estimates from the MS Registry, switching to alternative NMA sensitivities, excluding the price of JCV testing for natalizumab-IV and natalizumab-SC (not the biosimilar), reducing the natalizumab-SC treatment administration costs, and using mortality rates that vary with EDSS. Value of information analysis was used to assess the impact on parameter uncertainty and identify the most influential parameters. The Expected Value of Partial Perfect Information (EVPPI) was estimated for each of the NMA

treatment effects, all costs, all utilities, the MS registry baseline rates, the baseline discontinuation rate, and the baseline SAE rate.

Results

We included 42 studies (22,409 participants): 40 reported data for a general RRMS population and two were conducted in HARRMS. Six studies reported data separately for those with HARRMS. Only four studies evaluated Natalizumab or Natalizumab biosimilar, the technologies of interest for this appraisal; none provided data on those with HARRMS. AHSCT was only evaluated in people with HARRMS.

General RRMS population

All studies were considered to be sufficiently similar for inclusion in the NMAs. The fixed effect model gave the best fit to the data with little evidence of heterogeneity for all outcomes.

ARR (39 studies, 20,718 participants; 17 interventions)

Follow-up ranged from 4 to 36 (median 24) months. Most interventions were associated with a greater reduction in the risk of relapses compared to placebo (i.e., RR<1 AND 95% CrI excluding 1.00). There was no evidence of a difference between natalizumab and natalizumab biosimilar (RR 0.65 (95% CrI 0.34, 1.26). Seventeen (44%) studies were at low risk of bias, 15 (38%) had some concerns regarding risk of bias, and 7 (18%) were at high risk of bias. Sensitivity analysis restricted to studies at low risk of bias showed similar results.

Disease Progression (23 studies; 12 interventions)

Studies on teriflunomide, ponesimod and ofatumumab did not connect to the network and studies of natalizumab biosimilar and glatiramer acetate SC40 did not report on disease progression, and those on interferon beta 1a SC22 only reported data on CDP3. Fifteen studies (10, 824 participants; 11 interventions) reported CDP3 and fourteen studies (9,006 participants; 10 interventions) reported CDP6. Alemtuzumab, ocrelizumab, natalizumab, fingolimod, cladribineand peginterferon beta 1a were associated with a lower risk of both CDP3 and CDP6. Six studies were judged at low risk of bias, nine at some concerns and five at high risk of bias.

MRI Outcomes (20 studies; 12 interventions)

Follow-up ranged from 4 to 24 (median 24) months. There were no data on MRI outcomes for studies of ofatumumab, glatiramer acetate (SC40), ponesimod, teriflunomide, and peginterferon beta 1a. Data were only available for T2 lesions for interferon beta 1a (SC22).

Nineteen studies (9, 471 participants; 11 interventions) reported data on Gd+ lesions and seventeen studies (8,883 participants; 12 interventions) on T2 weighted lesions. All interventions were associated with a greater reduction in the risk of developing MRI lesions compared to placebo, with the exception of interferon beta 1a SC44 for T2 weighted lesions. There was no evidence of a difference between natalizumab and natalizumab biosimilar (HR 1.29 (0.69, 2.37) for Gd+ lesions or for T2 weighted lesions (HR 1.07 (0.73, 1.57)).

Adverse events (36 studies)

Follow-up ranged from 6 to 24 months (median 18 months) follow-up. Twenty four studies (14,513 participants; 16 interventions) reported data on **any adverse events** – data were not available for interferon beta 1a (SC22). Thirty one studies (18,149articipants; 15 interventions) reported data on **SAEs** – data were not available for interferon beta 1a (SC22), andnatalizumab biosimilar. There was no evidence of a difference in the risk of developing any AEs or serious AEs between any of the interventions and placebo. There was no evidence of a difference between natalizumab and natalizumab biosimilar 1.06 (0.79, 1.45) in the risk of any AEs; data were not available for serious AEs. Only eight studies (n=3,361) reported data on **treatment related adverse events**. These did not create a connected network and so an NMA was not possible. There was no evidence of a difference in AEs within any of the studies.

Twenty nine studies (17,892 participants) reported data on **AEs leading to treatment discontinuation**. These did not create a completely connected network – teriflunomide, ponesimod and ofatumumab did not connect to the network and data were not available for interferon beta 1a (SC22). Fingolimod, glatiramer acetate, interferon beta 1a, interferon beta 1b and peginterferon beta 1a were associated with an increased risk of treatment discontinuation compared with placebo. There was no evidence of a difference between natalizumab and natalizumab biosimilar (HR 0.48 (0.13, 1.76)).

Twenty studies were judged at low risk of bias for adverse events, eleven at some concerns and five at high risk of bias.

Quality of life

Only eight studies reported quality of life assessed using the EQ-5D or SF-36 tools. Interventions evaluated were cladribine, fingolimod, peginterferon beta and glatiramer acetate vs placebo and alemtuzumab vs interferon beta 1a. There was little evidence for a difference in quality of life in any of these studies.

HARRMS population

We had data for 6 studies that evaluated fingolimod, ocrelizumab, alemtuzumab, cladribine, beta-interferon, AHSCT, and placebo in people with HARRMS. Three studies were at high risk of bias, one had some concerns, and two were low-risk.

Five studies reported data on ARR. As there were no studies on natalizumab in people with HARRMS, we included one study that compared natalizumab with placebo in a population where participants were required to have had at least one relapse in the previous year and a very high proportion of participants (88%) had previously been treated with a DMT. A connected network for ARR was formed by combining two interferon beta 1a comparators. The network included six studies (2,162 participants) of seven interventions. All interventions except interferon beta 1a, were associated with a reduced ARR compared to placebo, with natalizumab and ocrelizumab ranking highest.

As we only had data on a limited number of interventions in HARRMS, to allow direct comparisons between RRMS and highly active populations, we conducted a sensitivity analysis in RRMS where we restricted the network to the eight interventions in the network

for ARR in the highly active population. Results were very similar, although 95% CrI were wider in the highly active population. CDP data were limited and disconnected, but all evaluated interventions reduced progression risk. MRI, QoL and adverse events outcomes were only evaluated in one or two studies and so there was insufficient information on these outcomes to draw conclusions.

Cost-effectiveness

The clinical review found no evidence on autologous haematopoietic stem cell transplantation so this was not included in the economic model. The NMA estimates in all RRMS were used for treatment effects on CDP6, ARR, SAEs, and discontinuation due to AEs, as only limited data were found for HARRMS.

Base case results used 1000 patients and 1000 samples while sensitivities used 100 patients and 100 samples; the lower number were found sufficient for stable results by convergence checks. Validation of EDSS severity over time found less severe trend that was explained by the comparator model mixing RRMS and SPMS patients and not using the latest DMT sequences.

Compared with natalizumab-IV, natalizumab biosimilar-IV and natalizumab-SC, all treatments had greater net benefit at £20-30,000/QALY, with the only exception being ocrelizumab. The natalizumabs had close to 0% chance of having highest net benefit at £20-30,000/QALY. Costs were generally higher on natalizumab than other treatments, though there was no difference in QALYs with 95% CrI overlapping. Natalizumab-IV has lower mean net benefit at £20-30,000/QALY than natalizumab biosimilar-IV, although the 95% CrI overlap. Natalizumab-SC has very similar mean net benefit to Natalizumab-IV. The 95% CrI for costs and QALYs on natalizumab biosimilar-IV also overlapped with those for natalizumab-IV suggesting no difference. Natalizumab-SC has very similar costs and QALYs to natalizumab-IV, again with no evidence of a difference.

Conclusions were unchanged under all sensitivities. EVPPI estimates indicated the parameters with greatest impact were the NMA treatment effects on ARR, CDP6, SAEs, and discontinuation. However, costs, utilities, and MS registry rates, also had substantial impact on the results indicating high parameter uncertainty.

Conclusions

There is no direct evidence on the effectiveness of natalizumab or its biosimilar in patients with highly active disease. Limited data indicate that both treatments show similar effectiveness in patients with RRMS. Comparisons of DMT effectiveness in people with highly active disease and general RRMS suggest that DMTs are at least as effective in the highly active population, although this is based on sparse data. Assuming natalizumab and its biosimilar follow this trend, they may also be effective in this group. However, trials specifically targeting this population are needed to confirm these assumptions.

The economic model used evidence on treatment effects in the general RRMS population and baseline rates in highly active RRMS. Natalizumab-IV, natalizumab biosimilar-IV and natalizumab-SC were not cost-effective compared to any of the included comparators in

highly active RRMS, with the only exception being ocrelizumab. The greatest decision uncertainty was found in the treatment effects, again supporting the need for trials targeting this population.

Study registration

The review was registered at PROSPERO (CRD42024556838).

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1 Background

Sections of this Chapter have been reproduced from the study's Protocol document, available at the NICE website.[1]

1.1 Multiple sclerosis

Multiple sclerosis (MS) is a chronic, inflammatory, neurological immune mediated inflammatory disease that affects the central nervous system (CNS), which includes the brain and spinal cord.[2] MS usually presents in early adult life and is the most common cause of non-traumatic disabling disease in young adults.[2-4] In MS, the immune system mistakenly attacks the protective covering of nerve fibres called myelin, causing inflammation and damage. This disrupts the normal flow of electrical impulses along the nerves. Inflammation can also lead directly to damage to axons, leading to their degeneration or loss. Axonal loss contributes significantly to the neurological symptoms and disability observed in people with MS.

The symptoms of MS vary widely and can include bladder and bowel dysfunction, cognitive changes, gait disturbance, fatigue, muscle weakness, numbness or tingling, difficulty with coordination and balance, and problems with vision.[2, 3]. It is not clear what causes MS, but a number of theories have been proposed. These include the “outside in” and “inside out” pathways. With the “outside in” model it is hypothesised that an unknown factor triggers the autoimmune response peripherally (outside the Central Nervous System (CNS)), instigating the immune system to begin to invade the CNS, starting the process of demyelination characteristic of MS. The “inside out” model suggest that primary damage of the myelin as the cause of MS, leading to an autoimmune attack which results in further inflammatory demyelination.[5] A number of factors have been associated with the risk of developing MS, these include genetic abnormalities, environmental factors such as vitamin D or ultraviolet B light (UVB) exposure, obesity, smoking and viral infection.[5, 6] More recently a compelling link has been established between Epstein-Barr virus (EBV) and MS – being negative for EBV protects against MS, whereas a history of exposure doubles the risk of developing MS.[6, 7] A number of genes have been found to be associated with MS. The main genetic risk is with the Human Leukocyte Antigen (HLA) HLA-DRB1*15, although genome wide association studies have identified over 200 independent genome-wide significant associations outside the major histocompatibility complex (MHC) and 32 within the MHC region and over 550 candidate risk genes.[8]

MS has a significant impact on individuals' quality of life and imposes a substantial burden on healthcare systems and society as a whole.[3] A recent cross-sectional study of almost 17,000 participants with MS from across 16 countries found that work capacity declined from 82% to 8%, and that quality of life declined from normal population values to less than zero, indicating that the negative aspects of an individual’s life outweigh the positive impacts, as disability became more severe with advancing disease.[3] MS may reduce life expectancy with a recent study estimating life expectancy to be 75.9 years in an MS population compared to 83.4 years in a population matched on sex, age, and region.[9] While there is currently no cure for MS, treatments are available to help manage symptoms, slow disease progression, and improve quality of life for individuals with MS.

1.2 Epidemiology of MS

MS is estimated to have a global prevalence of over 2.8 million cases (35.6 per 100 000 population), although this may be an underestimate due to the lack of data from large populations including China and India.[10] Incidence and prevalence is increasing in both developed and developing countries.[10]

Estimates of incidence vary across studies, with higher prevalence rates observed in regions further from the equator, particularly in Europe, North America, and parts of Australasia.[4, 6] A 2020 multi-national study reported a pooled incidence rate across 75 studies that provided data as 2.1 per 100 000 persons/year.[10] The prevalence of MS tends to increase with distance from the equator, although there are exceptions to this pattern.[6] The reasons for this geographic variation are not fully understood but may involve a combination of genetic, environmental, and lifestyle factors. Distance from the equator is also associated with UVB exposure which stimulates vitamin D production – low levels of vitamin D have been associated with MS.[6] Migration studies have shown that migrants from low risk countries (e.g. the West Indies) to Europe remain at low risk of developing MS, however children born to migrants in Europe are at high risk.[6] This suggests that environment over-rules genetics, suggesting that prevention should focus on environmental risk factors.

In the United Kingdom (UK), MS is a relatively common neurological condition, with an estimated prevalence of around 130 cases per 100,000 population, with an estimated 7,000 new cases each year.[11] The prevalence of MS in the UK is among the highest in Europe. MS affects people of all ages, but it is most commonly diagnosed in young adults, typically between the ages of 20 and 40. Women are about two to three times more likely to develop MS than men, although in the early 1900s the sex ratio was almost equal.[6] A reason for this change may be the changing prevalence of smoking in women over time – before the first world war very few women smoked. The incidence and prevalence of MS in the UK have been increasing over time, although this trend may be partially attributed to improvements in diagnostic methods and increased awareness of the condition.

1.3 Clinical pathway

1.3.1 Clinical presentation

MS is usually first suspected when a patient presents with what is known as a “clinically isolated syndrome” (CIS), this occurs as result of lesions in the brain or spinal cord and presentation will depend on the location of the lesion. The most frequent presentations include unilateral optic neuritis, brainstem syndromes (e.g. intranuclear ophthalmoplegia, vertigo, hearing loss, facial sensory disturbance) and focal sensory disturbance (e.g. limb paresthesias) although many other presentations exist.[6, 12]

1.3.2 Diagnosis of multiple sclerosis

The diagnosis of multiple sclerosis (MS) is primarily a clinical diagnosis, supported by investigations including imaging and cerebrospinal fluid (CSF) analysis. The key features required for a diagnosis of MS are dissemination in time and space – this involves looking for evidence of disease activity affecting different parts of the CNS across different points in time. Differential diagnosis of MS can be challenging, particularly in the early stages, as many other disorders have similar clinical presentations and paraclinical findings to MS.[13]

The 2022 NICE guidelines on the diagnosis and management of MS recommend that people suspected of having MS should be referred for diagnosis by a consultant neurologist or specialist under their supervision.[14]

Diagnostic criteria have evolved over time from the first criteria proposed by Jean-Martin Charcot as early as 1868[15] to the most recently published 2017 McDonald criteria.[16] The McDonald criteria were first developed by an international committee of neurologists and published in 2001.[17] These were updated in 2005, 2010 and most recently in 2017[16] – these are the current criteria recommended for diagnosis of MS by NICE. A 2024 update was announced at the recent ECTRIMS 2024 conference,[18] but these have not yet been published. These are expected to allow for an earlier diagnosis than previous versions of the criteria. Table 1 provides an overview of the 2017 McDonald criteria for diagnosing MS. These follow the principle of aiming to detect evidence of dissemination in time and space.

Table 1 2017 Revised McDonald criteria for diagnosing MS[16]

Number of attacks at clinical presentation	Number of lesions with objective clinical evidence	Additional data needed for diagnosis of MS
≥2	≥2	None
≥2	1 + clear cut historical evidence of a previous attacking involving a lesion in a distinct anatomical location	None
≥2	1	Dissemination in space demonstrated by additional clinical attack implicating a different CNS site *OR* by MRI
1	≥2	Dissemination in time demonstrated by an additional clinical attack *OR* by MRI *OR* demonstration of CSF-specific oligoclonal bands
1	1	Dissemination in space demonstrated by an additional clinical attack implicating a different CNS site OR by MRI AND Dissemination in time demonstrated by an additional clinical attack OR by MRI OR demonstration of CSF-specific oligoclonal bands

Magnetic resonance imaging (MRI) can be used to detect changes in white matter lesions in the brain. It is not sufficiently accurate to be used alone for the diagnosis of MS, but can be helpful in addition to clinical features.[19] CSF analysis involves detection of oligoclonal bands as a surrogate marker of dissemination in space.[20] The presence of oligoclonal bands (bands of immunoglobulin) provides evidence of local immunoglobulin synthesis which occurs most commonly in MS, but can also be found in other conditions and so the finding is not specific for the diagnosis of MS.[21] Findings of elevated CSF protein or significant pleocytosis or the presence of neutrophils is not typical of MS and so suggests an alternative diagnosis. The McDonald 2017 criteria allow for a greater role of MRI and CSF than previous versions, allowing for an earlier diagnosis of MS. This is particularly important as new, earlier aggressive treatments become available for MS; it is important to identify patients with MS so that they can receive treatment as soon as possible, but it is equally important that

people are not wrongly diagnosed with MS and given inappropriate treatment with these aggressive treatments.[22] Visually evoked potentials (VEP) have previously been suggested as useful for the diagnosis of MS. These are electrical signals recorded from the brain's occipital lobe in response to visual stimuli, used to assess the integrity of visual pathways, with an abnormal VEP suggesting a second lesion if the clinical presentation did not include the visual pathway. However, these are not included in the current diagnostic criteria due to insufficient evidence.[23]

1.3.3 Measurement of progression

Disease activity and progression are measured using MRI activity, incidence of relapses and short-term (3-6 month) progression in disability.[12] MRI measures of disease activity include the development of new T2 lesions, enlarging T2 lesions, and gadolinium-enhancing lesions. T2 lesions are areas of abnormal signal intensity seen on T2-weighted MRI scans, commonly indicating water content or inflammation in tissues. In MS, T2 lesions often represent areas of demyelination or damage in the brain and spinal cord, providing insights into disease activity and progression. Gadolinium-enhancing lesions are areas of the brain that show increased uptake of gadolinium-based contrast dye during MRI scans, indicating active inflammation. These lesions are used to identify active disease processes, distinguish new lesions from older ones, and to monitor treatment response. Disability is measured using the Expanded Disability Status Scale (EDSS) – this quantifies the accumulation of permanent disability. Scores range from 0 (no disability) to 10 (death) and are measured in incremental units of 0.5 (from EDSS 1). Scores are based on measures of impairment across the eight functional symptoms:[24]

1. Pyramidal Functions: weakness or difficulty in moving limbs
2. Cerebellar Functions: ataxia, loss of coordination, or tremor
3. Brain Stem Functions: problems with speech, swallowing, and nystagmus involuntary eye movement)
4. Sensory Functions: numbness or loss of sensations
5. Bowel and Bladder Functions
6. Visual (or Optic) functions
7. Cerebral (or Mental) Functions
8. Other Functions (neurologic findings)

To provide an accurate and reliable evaluation of confirmed disability progression (CDP) at 3 and 6 months, two consecutive examinations should be carried out by the same physician at least 3 and 6 months apart. Although EDSS is commonly used it does not capture some important aspects of the impact of MS, particularly on quality of life. It is also prone to bias as it is a subjective measure and so open to investigator bias and is also heavily influenced by mobility.

1.3.4 Classification of MS

MS presents on a continuum from relapsing to progressive disease, with distinctions currently made between different types of disease. Some see this as an artificial distinction as they force cases into distinct boxes, which does not reflect the continuum of illness.[6] Most cases of MS (85-90%) are characterised by relapses followed by periods of remission – known as “relapsing remitting MS” (RRMS). A relapse generally develops over a period of hours to days, then reaches a plateau lasting several weeks, followed by a period of gradual

recovery. The nature of the relapse is dependent on the region of the CNS affected by the acute demyelinating lesion, and also by the extent of the inflammation.[4] Although initial relapses can lead to complete recovery, there is often some damage left behind by the relapse, with overall disability increasing slightly after each relapse.[25] As neuronal damage increases, recovery from disability becomes incomplete leading to further disability.[6] RRMS is further subcategorised depending on disease activity and response to treatment. There is a lack of consensus regarding the definitions for the varying subtypes of disease, with different appraisals and studies using slightly different definitions. Table 2 provides an overview of the different subclassification of RRMS, with suggested definitions for each. The population of interest for this appraisal is "highly active disease" (highlighted blue in the table). We provide a very broad definition for this population to encompass most of the variety of different definitions used in existing appraisals and studies.

Table 2 Overview of subclassifications of RRMS[26]

Classification	Definition
Active disease	≥Two clinically significant relapses within the last 2 years. (Any motor relapse, any brainstem relapse, a sensory if it leads to functional impairment, a relapse leading to sphincter dysfunction, optic neuritis, intrusive pain lasting more than 48 hours)
Highly active disease	No consensus definition; previous appraisals for NICE have used different definitions. We will use the following broad definition for this appraisal to encompass the variety of different definitions used in existing trials: *Unchanged or increased clinical or radiological evidence of disease activity despite treatment with at least one Disease Modifying Therapy (DMT)*
Rapidly evolving severe (RES) disease	≥Two disabling relapses in 1 year and MRI changes (one or more gadolinium-enhancing lesions or a significant increase in T2 lesion load compared with a previous MRI). A disabling relapse is defined as any relapse which fulfils one or more of the following criteria: • Affects the patient's social life or occupation, or is otherwise considered disabling by the patient • Affects the patient's activities of daily living as assessed by an appropriate method • Affects motor or sensory function sufficiently to impair the capacity or reserve to care for themselves or others • Needs treatment/hospital admission.[26]

After 10-15 years RRMS typically develops into "secondary progressive MS" (SPMS), characterised by a gradual progression from discrete relapses to disease that progresses slowly.[23] A smaller proportion have a progressive onset from the start, known as "primary progressive MS" (PPMS). The proportion of patients with PPMS has decreased over time, but this may be an artificial change, caused by patients being more commonly labelled as having RRMS so that they are eligible for some of the newer treatments,[6] or be a result of better ascertainment of relapses leading to more people being identified as having RRMS. PPMS is more common in those presenting in later life (over age 60 years).[4]

1.3.5 Management of MS

Management of MS typically involves a multidisciplinary approach, including medical treatment to manage symptoms and modify disease progression, rehabilitation therapies, and support services to address the physical, cognitive, and emotional challenges associated with the condition. The pathway may vary depending on the subtype of MS, disease

severity, individual patient factors, and treatment goals. The MS treatment pathway is dynamic and individualized, requiring ongoing collaboration between patients, healthcare providers, and interdisciplinary teams to optimize outcomes and quality of life for individuals living with MS. NICE guidelines recommend that people with MS should have a comprehensive review of all aspects of their care at least once a year.[12, 14]

Symptomatic management focuses on alleviating symptoms associated with MS, such as fatigue, mobility problems, spasticity, oscillopsia, emotional lability, pain, cognitive and memory problems, ataxia, tremor and dystonia. Symptomatic treatments may include medications, physical therapy, occupational therapy, speech therapy, cognitive rehabilitation, assistive devices, and lifestyle modifications.[14] Acutely, relapses are often treated with corticosteroids and, sometimes, plasma exchange.[27]

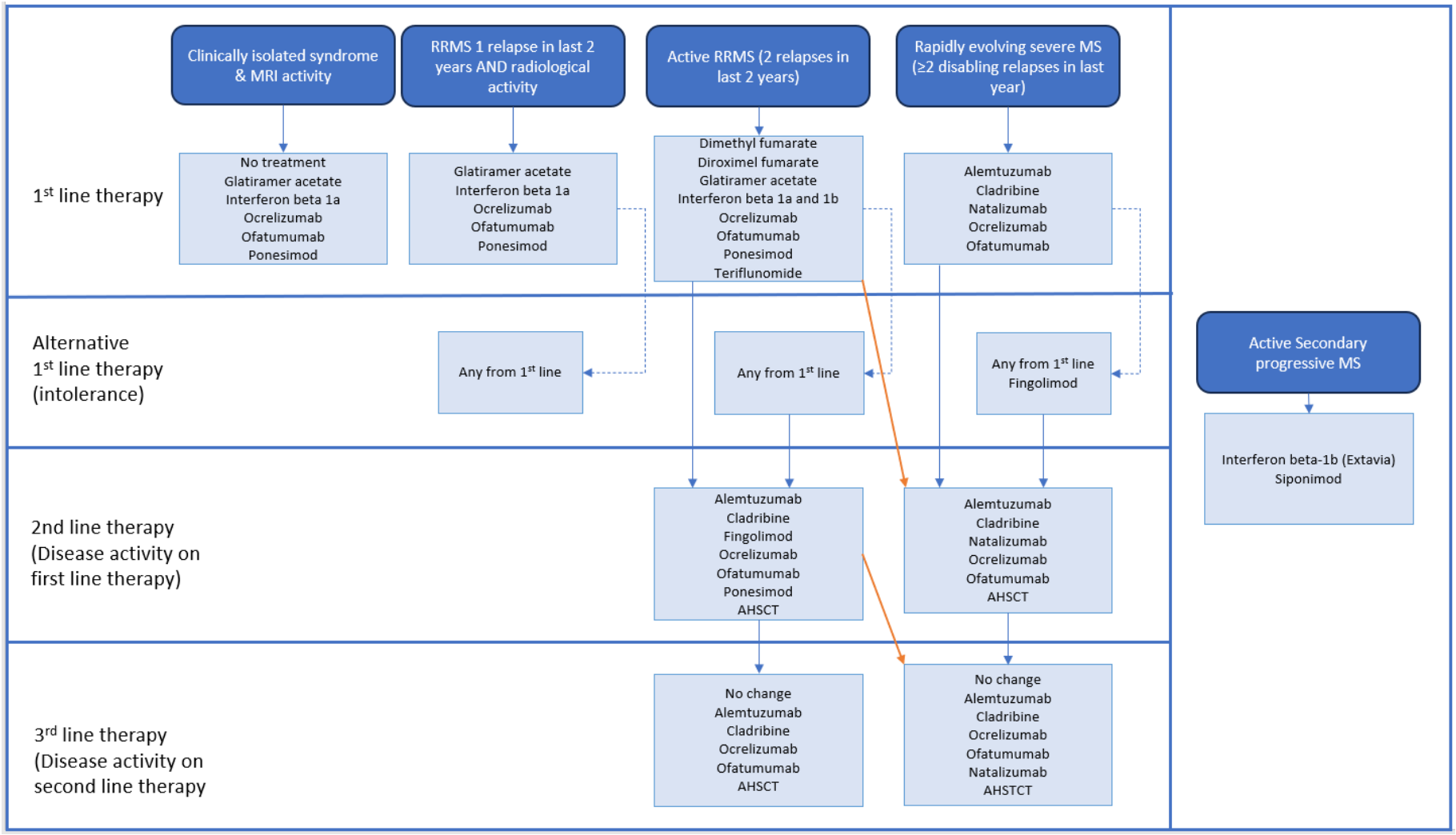
Disease-modifying therapies (DMTs) are the cornerstone of treatment for relapsing forms of MS. DMTs aim to reduce the frequency and severity of relapses, delay disability progression, and decrease the number of lesions observed on MRI scans.[12] They work by modifying the course of MS by supressing or modulating immune function. Various DMTs are available, including injectable medications, oral agents, and infusion therapies, each with different mechanisms of action and side effect profiles. Interferon beta-1b was the first DMT to be approved by the Federal Drugs Agency (FDA) in 1993. This was followed by interferon beta-1b and glatiramer acetate. These drugs were generally well tolerated and have a modest impact on the frequency of relapses.[28] Prior to this a variety of immunosuppressive agents were used to treat MS including azathioprine, methotrexate, mycophenolate mofetil, intravenous immunoglobulin, and corticosteroids.[28]

More recently many MS specific DMTs have become available.[28]
Table 3 provides an overview of the DMTs that have been appraised by NICE. It also highlights which DMTs are included in the scope for this appraisal – interventions and comparators are shown in cells shaded blue in the table, interventions are also highlighted in bold. NHS England have developed a treatment algorithm for DMTs within the NHS. Different treatment options are recommended based on initial presentation.[29] The recommendations for RRMS are summarized in Figure 1. An additional treatment option is *autologous haematopoietic stem cell transplantation*. This involves collecting a patient's healthy stem cells from the blood or bone marrow before treatment, storing this and then giving it back to the patient after treatment. A growing body of evidence suggests that this can induce prolonged remission in patients with RRMS.[28]

Patients who progress to SPMS are managed with Interferon beta-1b (Extavia) or Siponimod if they meet the following starting criteria:

- Patient is able to walk 10 m or more (EDSS less than 7.0)
- >18 years-old
- No contraindications
- Patient has been informed of and agreed to stopping criteria
- For Siponimod, there is also a requirement of active disease (relapses or imagine features of inflammatory activity).[30]

Figure 1 NHS England treatment algorithm for MS DMTs



Orange arrows show treatment pathways for patients with active RRMS who develop RES
AHSCT: autologous haematopoietic stem cell treatment.

Table 3 Overview of DMTs for adults with MS together with details of marketing authorisation and NICE recommendations

Pale blue highlighting shows interventions and comparators included within the scope of this appraisal

Drug name	Mechanism of Action	Administration route and frequency	Marketing authorisation	Related NICE TA	NICE recommendation
Recommended for RRMS					
Glatiramer Acetate	Not fully known	SC injection, once daily or 3 times weekly	Relapsing forms of multiple sclerosis.	TA527[31]	Recommended for treating RRMS
Interferon beta-1a	Not fully known	IM injection, once Weekly or SC injection, 3 times weekly	Relapsing multiple sclerosis. In clinical trials, this was characterised by two or more acute exacerbations (relapses) in the previous three years without evidence of continuous progression between relapses.	TA527[31]	Recommended for treating RRMS
Peginterferon beta-1a	Not fully known	SC injection, every 2 weeks	Relapsing remitting multiple sclerosis.	TA624[32]	Recommended for treating RRMS
Interferon beta-1b (Extavia)	Not fully known	SC injection, every other day	Relapsing remitting multiple sclerosis and two or more relapses within the last two years.	TA527[31]	Recommended for treating RRMS if person has had 2 or more relapses with past 2 years. *Currently not available in the UK*
Recommended for RRMS in specific situations or specific subtypes					
Ocrelizumab	Anti-CD20 mAb	IV infusion, every 6 months	Adult patients with relapsing forms of multiple sclerosis (RMS) with active disease defined by clinical or imaging features.	TA533[33]	Recommended for active RRMS only if alemtuzumab is contraindicated or otherwise unsuitable
Natalizumab (Tysabri)	α4β1 integrin inhibitor	IV infusion, every 4 weeks can also be given subcutaneously	Highly active RRMS: • Rapidly evolving severe RRMS defined by 2 or more disabling relapses in one year, and with 1 or more Gadolinium enhancing lesions on brain Magnetic Resonance Imaging (MRI) or a	TA127[34]	Recommended for rapidly evolving severe RRMS

Drug name	Mechanism of Action	Administration route and frequency	Marketing authorisation	Related NICE TA	NICE recommendation
			significant increase in T2 lesion load as compared to a previous recent MRI. OR • Highly active disease despite a full and adequate course of treatment with at least one DMT		
Natalizumab biosimilar (Tyruko)	α4β1 integrin inhibitor	IV infusion, every 4 weeks	Highly active RRMS: • Rapidly evolving severe RRMS defined by 2 or more disabling relapses in one year, and with 1 or more Gadolinium enhancing lesions on brain Magnetic Resonance Imaging (MRI) or a significant increase in T2 lesion load as compared to a previous recent MRI. OR • Highly active disease despite a full and adequate course of treatment with at least one DMT	NA	Recommended as per Natalizumab (Tysabri) under NICE's biosimilar policy
Diroximel fumarate (Almirall)	Nuclear factor (erythroid derived 2)−like 2 pathway inhibitor	Oral, twice daily	Adult patients with relapsing–remitting multiple sclerosis.	TA794[35] TA320[36]	Recommended for active RRMS only if they do *not* have highly active or rapidly evolving severe relapsing–remitting multiple sclerosis
Dimethyl fumarate	Promotes anti-inflammatory activity and can inhibit expression of pro-inflammatory cytokines and	Oral, twice daily	Indicated for the treatment of adult patients with relapsing remitting multiple sclerosis	TA320[36]	Recommended for active RRMS, only if: they do not have highly active or rapidly evolving severe relapsing-remitting multiple sclerosis, and the manufacturer provides dimethyl fumarate with the

Drug name	Mechanism of Action	Administration route and frequency	Marketing authorisation	Related NICE TA	NICE recommendation
	adhesion molecules				discount agreed in the patient access scheme.
Teriflunomide	Inhibits the enzyme dihydroorotate dehydrogenase (DHODH)	Oral, 14 mg once daily	Approved for the treatment of RRMS in adults and children aged 10 years and older.	NICE TA303[37]	Recommended for active RRMS only if they do not have highly active or rapidly evolving severe RRMS and the manufacturer provides teriflunomide with the discount agreed in the patient access scheme.
Cladribine	Not fully known	Oral, 4-5 days over 2-week treatment courses	Adult patients with highly active relapsing multiple sclerosis (MS) as defined by clinical or imaging features	NICE TA616[38]	Recommended for highly active MS only if the person has rapidly evolving severe RRMS or disease that has responded inadequately to treatment with DMT
Recommended for previously treated RRMS					
Alemtuzumab	Anti-CD52 mAb	IV infusion, once daily	Adult patients with relapsing remitting multiple sclerosis (RRMS) with active disease defined by clinical or imaging features.	TA312[39]	Recommended for highly active RRMS despite a full and adequate course of treatment with at least 1 disease-modifying therapy OR rapidly evolving evere RRMS
Fingolimod	Sphingosine-1-phosphate inhibitor	Oral, once daily	Indicated as single disease modifying therapy in highly active relapsing remitting multiple sclerosis for the following adult patient groups: • Patients with highly active disease despite a full and adequate course of treatment with at least one disease modifying therapy or • Patients with rapidly evolving severe relapsing remitting multiple sclerosis defined by 2 or more disabling relapses in one year, and with 1 or more Gadolinium enhancing lesions on brain MRI or a	TA254[40]	Recommended for highly active RRMS if they have an unchanged or increased relapse rate or ongoing severe relapses compared with the previous year despite treatment with beta interferon

Drug name	Mechanism of Action	Administration route and frequency	Marketing authorisation	Related NICE TA	NICE recommendation
			significant increase in T2 lesion load as compared to a previous recent MRI		
Ofatumumab	Anti-CD20 mAb	SC injection, every 4 weeks	Adult patients with relapsing forms of multiple sclerosis (RMS) with active disease defined by clinical or imaging features.	TA699[41]	Recommended for previously treated active RRMS, only if alemtuzumab is contraindicated or otherwise unsuitable
Ponesimod	Sphingosine-1-phosphate inhibitor	Oral, once daily	Adult patients with relapsing forms of multiple sclerosis (RMS) with active disease defined by clinical or imaging features.	TA767[42]	Recommended for previously treated active RRMS
Cladribine	Not fully known	Oral, 4-5 days over 2-week treatment courses	Adult patients with highly active relapsing multiple sclerosis (MS) as defined by clinical or imaging features	NICE TA616[38]	Recommended for highly active MS only if the person has rapidly evolving severe RRMS or disease that has responded inadequately to treatment with DMT
Recommended for SPMS					
Siponimod	Sphingosine 1-phosphate receptor modulator	Oral, once daily	Adult patients with secondary progressive multiple sclerosis (SPMS) with active disease evidenced by relapses or imaging features of inflammatory activity.	TA656[30]	Recommended as an option for treating SPMS with evidence of active disease (that is, relapses or imaging features of inflammatory activity)
Interferon beta-1b (Extavia)	Not fully known	SC injection, every other day	Patients with secondary progressive multiple sclerosis with active disease, evidenced by relapses.	TA527[31]	Recommended for SPMS with continuing relapses
Recommended for PPMS					
Ocrelizumab	Anti-CD20 mAb	IV infusion, every 6 months	Adult patients with early primary progressive multiple sclerosis (PPMS) in terms of disease duration and level of disability, and with imaging features characteristic of inflammatory activity.	TA585[43]	Recommended for treating early PPMS with imaging features characteristic of inflammatory activity
Not recommended					

Drug name	Mechanism of Action	Administration route and frequency	Marketing authorisation	Related NICE TA	NICE recommendation
Interferon beta-1b (Betaferon)	Not fully known	SC injection, every other day	• Patients with a single demyelinating event with an active inflammatory process, if it is severe enough to warrant treatment with intravenous corticosteroids, if alternative diagnoses have been excluded, and if they are determined to be at high risk of developing clinically definite multiple sclerosis. • Patients with relapsing-remitting multiple sclerosis and two or more relapses within the last two years). • Patients with secondary progressive multiple sclerosis with active disease, evidenced by relapses.	TA527[31]	**Not recommended**
Ozanimod	Sphingosine 1-phosphate receptor modulator	Oral, once daily	Adult patients with relapsing remitting multiple sclerosis (RRMS) with active disease as defined by clinical or imaging features	TA706[44]	**Not recommended** for treating active RRMS

2 Decision Problem

Sections of this Chapter have been reproduced from the study's Protocol document, available at the NICE website.[1]

2.1 Technologies and population of interest for this appraisal

The technologies of interest for this appraisal are Natalizumab (Tysabri, Biogen) and natalizumab biosimilar (Tyruko, Sandoz). Natalizumab (Tysabri) has a marketing authorization for subcutaneous and intravenous administration, whereas natalizumab biosimilar (Tyruko) has a license for intravenous administration only. Both drugs have been licensed as single disease modifying therapy (DMT) in adults with highly active relapsing remitting multiple sclerosis for the following people:

- People with rapidly evolving severe RRMS defined by 2 or more disabling relapses in one year, and with 1 or more Gadolinium enhancing lesions on brain Magnetic Resonance Imaging (MRI) or a significant increase in T2 lesion load as compared to a previous recent MRI.

OR

- People with highly active disease despite a full and adequate course of treatment with at least one disease modifying therapy

NICE already recommends natalizumab as a first-line treatment option for people with rapidly evolving severe relapsing–remitting multiple sclerosis (NICE TA127;[34]
Table 3) covering the first part of the population above. This appraisal therefore focuses only **on highly active relapsing-remitting multiple sclerosis after at least one disease modifying therapy**. Table 2 provides a summary of how different subtypes are classified.

2.2 Comparators for this appraisal

The comparator for this appraisal is standard care without natalizumab or natalizumab biosimilar. This includes the following interventions:

- Glatiramer acetate
- Interferon beta 1a
- Interferon beta 1b
- Alemtuzumab
- Cladribine tablets
- Fingolimod
- Ocrelizumab. *The NICE scope*[45] *suggested that this should only be if alemtuzumab is contraindicated. However, our clinical advisors suggested that this is not reflective of this drug is used in clinical practice and so we will not apply this restriction for our appraisal.*
- Ofatumumab
- Ponesimod
- Autologous haematopoietic stem cell transplantation

3 Aim and Objectives

Sections of this Chapter have been reproduced from the study's Protocol document, available at the NICE website.[1]

The overall aim of this assessment was to appraise the clinical and cost effectiveness of natalizumab (Tysabri) and natalizumab biosimilar (Tyruko) within their marketing authorisations for treating highly active RRMS after at least one disease modifying therapy.

To address this aim, we completed the following:

1. Systematic literature review (SLR) of treatments for highly active RRMS after at least one disease modifying therapy
2. Network meta-analysis to estimate the clinical effectiveness and safety of treatments for highly active RRMS after at least one disease modifying therapy
3. Economic modelling to assess the cost-effectiveness of treatments for highly active RRMS after at least one disease modifying therapy

4 Assessment of clinical effectiveness

Sections of this Chapter have been reproduced from the study's Protocol document, available at the NICE website.[1]

We conducted an SLR to summarise the effectiveness of treatments for relapsing-remitting multiple sclerosis after at least one disease modifying therapy. The SLR followed the principles outlined in the Centre for Reviews and Dissemination (CRD) guidance for undertaking reviews in health care and the NICE Health Technology Evaluations Manual.[46, 47] and is reported according to the PRISMA 2020[48] and PRISMA NMA statements.[49]

4.1 Selection criteria

Studies that met the following criteria were eligible for inclusion:

4.1.1 Participants

The population of interest for this appraisal is people with highly active RRMS who have received at least one previous DMT (see Table 3). As we did not expect to find studies for all interventions of interest in this specific sub-population, inclusion for the SLR was broadened to include all studies in patients with RRMS. RRMS was defined broadly to include studies of "relapsing MS". Studies were included if at least 90% of the participants had RRMS or if data could be extracted for this sub-population of interest.

4.1.2 Interventions

The two interventions of interest for this appraisal are **natalizumab** (300 mg IV infusion, every 4 weeks can also be given subcutaneously – referred to as natalizumab IV300 or natalizumab SC) and **natalizumab biosimilar** 300 mg IV infusion, every 4 weeks. To allow comparison with standard care we also included trials that evaluated the treatments summarised in Table 4. This also shows the intervention label used in tables and figures for each of these specific intervention doses.

Table 4 Overview of eligible comparator interventions

Treatment	Dose	Frequency	Admin-istration	Label in tables and figures
Alemtuzumab	12mg	Month 1 - daily for 5 days in month 1; month 13 - daily for 3 days	IV	Alemtuzumab IV12
Autologous haematopoietic stem cell transplantation				AHSCT
Cladribine	3.5 mg/kg	4-5 days over 2-weeks	Oral	Cladribine O3.5
Fingolimod	0.5 mg	once daily	Oral	Fingolimod O0.5
Glatiramer acetate	20 mg	Daily	SC	Glatiramer acetate SC20
Glatiramer acetate	40 mg	Daily	SC	Glatiramer acetate SC40
Interferon beta 1a (avonex)	30 mcg	Weekly	IM	Interferon beta 1a IM30
Interferon beta 1a (rebif)	22 mcg	3 times weekly	SC	Interferon beta 1a SC44
Interferon beta 1a (rebif)	22 mcg	3 times weekly	SC	Interferon beta 1a SC44
Interferon beta 1b	250 mcg	every other day	SC	Interferon beta 1b IM 2 50
Ocrelizumab	600 mg	every 6 months	IV	Ocrelizumab IV600
Ofatumumab	20 mg	every 4 weeks	SC	Ofatumumab SC20
Peginterferon beta 1a	125 mcg	every 2 weeks	SC	Peginterferon beta 1a S C125

Treatment	Dose	Frequency	Admin-istration	Label in tables and figures
Ponesimod	20 mg	Once daily	Oral	Ponesimod O20

SC: subcutaneous; IV: intravenous; IM: intra-muscular

Studies were required to compare one of the interventions above to an alternative intervention listed above, or to placebo, so that only studies that are informative for the network were included. We excluded studies that only compared different doses, modes of administration, or manufacturers of the same intervention unless these were needed to create a connected network.

4.1.3 Outcomes

Studies that report data on any of the following outcomes were eligible for inclusion:

- Relapse rate
- MRI measurements
- Disability progression
- Disease progression
- Adverse effects of treatment
- Health-related quality of life

4.1.4 Study design

We restricted inclusion to randomised controlled trials; open label extension studies were not eligible. No language or publication restrictions were applied.

4.2 Identification of studies

4.2.1 Literature searches

Studies/reports were identified using bibliographic and non-bibliographic search methods following guidance in the NICE technology appraisal manual.[47]

Bibliographic searching

The following databases were searched:

- MEDLINE (Ovid) 1946 to April 30, 2024
- Embase (Ovid) 1974 to 2024 April 30

The search strategy was written by one researcher and checked by another, taking the following form:

1. Terms for relapsing remitting MS
2. Terms for Interventions listed in section 4.1.2
3. The Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity- and precision-maximizing version (2008 revision) supplemented with the Cooper P3 filter[50, 51]
4. 1 and 2 and 3

The bibliographic search strategy was not limited by date of publication or by language. The searches strategies are reported in

Appendix 1.

Non-bibliographic search methods

Completed and ongoing trials were identified through searches of the following trials registry resources:

- ClinicalTrials.gov via www.clinicaltrials.gov; and
- World Health Organisation (WHO) International Clinical Trials Registry Platform (ICTRP) via www.who.int/clinical-trials-registry-platform.

For included studies, the study's web page on the trials registry resource was re-checked for data (published results) or linked publications.

Whilst SLRs were not eligible for inclusion, any SLRs published in the last three years (2021-current) and which aligned with our scope, were retained. We checked the studies included in each review to identify any studies not identified by our searches.

NICE requested submissions from Companies with technologies in scope for this appraisal (See Table 3). We checked the submissions for studies (and study data) which align with our inclusion criteria. Any studies identified through this process were tabulated to show where they contributed to our review or why they were excluded (Appendix 2).

4.2.2 Managing the searches

Search results were exported to EndNote 20 for de-duplication. We compared the studies and study reports from the mapping of TAs to our search results. Search results were exported to Microsoft Access for screening.

4.2.3 Studies included in existing TAs

We reviewed existing TAs of interventions or comparators of interest for this appraisal to determine whether they had included any studies that were not identified by our searches. We also reviewed existing TAs for additional data not available in study reports. Where additional relevant data were found, these were included in the review.

4.3 Review strategy

4.3.1 Title and abstract screening

Titles and abstracts from the literature searches were screened independently by two reviewers using a Microsoft Access database developed specifically for this review. At this stage all records that evaluated one of the interventions of interest in the broad population of patients with RRMS were retrieved. Full copies of all reports considered potentially relevant were obtained and moved to the inclusion assessment stage. Studies included in existing TAs moved straight to the inclusion assessment stage.

4.3.2 Full text inclusion assessment

Full text studies, including all reports included in existing TAs, were assessed for inclusion against the criteria specified in section 4.1. At this stage of the review process, we moved our review management to a new online systematic review management software – Nested Knowledge (www.nested-knowledge.com). One reviewer assessed studies for inclusion.

Where studies were excluded, the reason for exclusion was recorded. For included studies, we recorded basic information for each study including language of report, MS population subtype (e.g. RRMS, SPMS, PPMS, other, mixed), whether data were available for the highly active RRMS sub-population, interventions evaluated, whether outcomes of interest were reported, study design, and study name or trial registry ID. Inclusion assessment and recorded information was checked by a second reviewer. Any disagreements were resolved by consensus or discussion with a third reviewer.

4.3.3 Mapping reports to studies

All reports of studies that met the review inclusion criteria progressed to the mapping stage. This stage linked multiple reports of the same study. The information recorded at the inclusion assessment stage was used to help identify linked reports. We identified a "primary report" for each study, this was the study that reported the most complete trial data and results. Other reports, including NICE technology appraisals that included the primary report, were labelled as secondary reports and were linked within Nested Knowledge. For each linked report we recorded whether data were extracted from the report, and if so, what data were extracted.

4.3.4 Data extraction

Data were extracted using standardised data extraction forms developed in Nested Knowledge (www.nested-knowledge.com). Data extraction forms were piloted on a small sample of papers and adapted as necessary. Data were extracted by one reviewer and checked in detail by a second reviewer. Any disagreements were resolved by consensus or discussion with a third reviewer. Nested knowledge offers some artificial intelligence (AI) features that we used to support data extraction of some baseline data. It incorporates a feature known as "smart tag" recommendations that uses GPT 4, a large language model from OpenAI, to provide automatic highlighting of full texts based on our configured "tags" (fields to extract data to). This was not used to replace human reviewers but as a tool to streamline the data extraction process. Both reviewers read the full text and relevant supplementary materials of all included studies in detail to identify and extract relevant data.

Baseline data

Data were extracted on the following:

- Study phase
- Funding sources (public, industry, mixed)
- Full text or conference abstract
- NCT number
- Study location
- Population
    - Criteria used to diagnose MS
    - Proportion of participants with RRMS
    - RRMS subtype
    - Previous treatment
- Interventions
    - Treatment names

    - Mode of administration
    - Dose
    - Frequency
- Number of participants (eligible, randomised and treated)
- Age
- Sex
- Ethnicity
- EDSS score
- Time from diagnosis of MS to study entry
- Annual relapse rate at baseline

For continuous measures, we extracted mean and standard deviation (SD) in each intervention group – this was reported by the majority of studies. If standard error (SE) was reported instead of the SD, we extracted the SE and sample size (n) and used this to calculate the SD by multiplying the SE by √n. If the SD and SE were not reported we extracted the range or interquartile range, where reported.

If the mean relapse rate was reported over a time period of different than one year, we calculated the mean annual relapse rate by dividing the reported relapse rate by the time period over which the relapse rate was calculated.

Outcome data

Where possible results data were extracted for both the sub-population of interest (highly active RRMS) and for the overall RRMS population. Data were extracted for the time points closest to 12, 24 and 36 months follow-up reported in each study. Where data were only reported graphically, data were extracted from the graphs where possible.

Annualised relapse rate

Studies used different definitions of a relapse, where reported we extracted data on the definition used in each study. We extracted the most appropriate data reported in each study to calculate the annual relapse rate ratio and 95% confidence interval, based on the following hierarchy:

I. Rate ratios (RR) together with 95% CIs and p-values for comparisons between groups together with details on the methods of analysis, any variables controlled for in the analysis and the test statistic. The reported rate ratios for ARR were converted to the log rate ratio scale (i.e. a log link). The standard error for the log rate ratio was calculated by assuming normality on the log scale and assuming the upper and lower 95% confidence intervals are separated by $2 \times 1.96 \times SE$. If the log rate ratio of an event on arm k relative to arm 1 in trial i is denoted y_{ik} and its standard error se_{ik} ($k \geq 2$) we use the Normal likelihood

$$y_{ik} \sim N(\theta_{ik}, se_{ik}^2)$$

Using the identity link the linear predictor is

$$\theta_{ik} = \delta_{ik}$$

II. Annual relapse rate in each intervention group, together with 95% CIs and p-value for comparisons between groups. For such studies we therefore modeled the absolute log hazard rate for CDP3/6 or log rate for ARR for each arm h_{ik} with standard error hse_{ik}^2, again calculated using $2 \times 1.96 \times SE$, as

$$h_{ik} \sim N(\theta_{ik}, hse_{ik}^2)$$

With link function

$$\theta_{ik} = \mu_i + \delta_{i,bk} I_{k \neq 1}$$

Where μ_i represents the log rate on baseline arm $k = 1$.

III. Annual relapse rate in each intervention group together with number of events per arm for comparisons between groups, together with details on the methods of analysis, any variables controlled for in the analysis and the test statistic. For these studies we used use rates to calculate rate ratio and SE(lnRR) (using rate and number of participants to calculate number of events), as follows,[52] where E represents the number of events:

$$RR = \frac{ARR_1}{ARR_2}$$

$$SE = \sqrt{\frac{1}{E_1} + \frac{1}{E_2}}$$

The calculated rate ratios were also converted to the log rate ratio scale as shown in I.

Disability progression

We extracted data on:

- 3 months confirmed disability progression (CDP3)
- 6 months confirmed disability progression at (CDP6)

These outcomes refer to the proportion of participants who have confirmed disability progression based on their EDSS scores sustained for at least 3 (CDP3) or 6 months (CDP6). Disability progression is usually defined as an increase in EDSS by ⩾1.0 point from the baseline EDSS if the baseline EDSS is ⩽5.5 or an increase of ⩾0.5 points if the baseline EDSS is >5.5.[53] However, studies may use different definitions and so we also extracted the exact definition used in each study.

We extracted data on the following, where reported:

- Hazard ratios for time to CDP3 and time to CDP6 together with 95% CIs and p-values
- Proportion of participants with CDP3 and CPD6.

Reported HRs were treated in the same way as RRs for ARR, as shown in I. When HRs were not reported they were estimated with a hazard rate analysis of event frequencies in relation to time at risk (when follow-up time was available), or from 2x2 tables of event numbers using complementary log-log (cloglog) transformations, assuming proportional hazards,[52] using

$$HR = \frac{E_2 T_1}{E_1 2}$$

Where E is number of events and T is persons-years at risk, and we estimated the SE of the log hazard rate or log rate using[54]

$$SE = \sqrt{\frac{1}{E_1} + \frac{1}{E_2}}$$

[54]

Calculated HRs were treated in the same way as calculated RRs for ARR.

MRI outcomes

We only extracted data on the following MRI outcomes, where reported:

- Proportion of participants with gadolinium enhancing (gd+) T1 lesions. We were primarily interested in the total number of lesions.
- Proportion of participants with T2 lesions. We were primarily interested in the those with new or enhancing T2 lesions.

Studies reported slightly different definitions of gd+ lesions and new or enlarging T2 lesions – we extracted details on how these were defined in each study.

We used data on the proportion of participants with lesions in each intervention group and follow-up time to calculate hazard ratios in the same way as it was done for disability progression.

Adverse events

We extracted data on the proportion of participants in each intervention group that experienced the following categories of adverse events (AEs):

- Any AEs
- Treatment related AEs
- Discontinuation due to AEs
- Serious AEs
- Grade 3 or 4 AEs

We used data on the proportion of participants with each type of AEs in each intervention group and follow-up time to calculate hazard ratios in the same way it was done for disability progression. For zero count cells, a continuity correction was applied where a constant (0.5) was added to each cell of the 2x2 table.

We also extracted data on the AEs reported, but did not record the number of participants with each specific AE.

Health-related quality of life

We only extracted data on quality of life measured using the EuroQol 5 dimensions (EQ-5D) or Self-Reported SF-36 scales, but also noted where data were available for other scales. We extracted means/medians together with ranges, standard deviations (SD), standard errors (SE) and/or confidence intervals (CIs) at baseline and follow-up. Summary effect estimates (e.g. mean difference (MD)) together with 95% CIs and p-values for comparisons were extracted.

4.3.5 Quality assessment strategy

The methodological quality of included RCTs was assessed using the updated Cochrane Risk of Bias Tool (RoB-2).[55] This considers the risk of bias across five domains: randomisation process, deviations from the intended interventions, missing outcome data, measurement of the outcome and selection of the reported result. Domains are rated as "low risk of bias", "high risk of bias" or "some concerns". An overall risk of bias assessment is generated based on the "worst" risk of bias in any individual domain i.e. if one domain is judged at high risk of bias the whole study is considered at high risk of bias. Risk of bias assessment was done at the outcome level for the outcomes of ARR, disease progression, MRI outcomes and safety outcomes. Any disagreements were resolved by consensus or discussion with a third reviewer.

4.3.6 Methods of data synthesis

For each population and outcome, we present a narrative summary of included studies. This includes a summary of study characteristics (e.g. sample size, geographical location, publication year) and baseline participant characteristics (proportion of participants that did not have RRMS, age, sex, ethnicity, EDSS scores, annual relapse rate, disease duration, proportion of patients who had received previous DMT treatment) and risk of bias.

Network Meta-Analysis

To compare the efficacy and safety of treatment options using the available trial information, Bayesian Network Meta-Analyses (NMA) was conducted. NMA strengthens inference concerning the relative effect of two treatments by including both direct and indirect comparisons while respecting randomisation. Most treatments were not compared in head-to-head RCTs, and NMA allowed for the use of indirect information to make such comparisons. General details of NMA are given in NICE Decision Support Unit Technical Support Document 2.[56] Interventions with different doses were considered as separate nodes. An exception was made for the analysis for the HARRMS population, where beta-interferons 1a were grouped to create a single node to allow the network to connect. This is similar to the approach of TA767 on posenimod.[42] Table 5 provides an overview of each intervention included in the NMA.

Random and fixed effects analyses were performed. For the random-effects models the trial-specific log ratios come from a normal distribution with an estimated heterogeneity variance which is assumed to be the same for all treatment comparisons. For the fixed-effects model the log ratios were assumed to be the same across studies, which is equivalent to setting the between-trial heterogeneity to zero thus assuming homogeneity of the underlying true treatment effects.

Vague priors (Fixed effects model: prior_intercept = normal (0, scale = 10), prior_trt = normal (0, scale = 10), random effects model: prior_intercept = normal (0, scale = 10), prior_trt = normal (0, scale = 10), prior_het = half_normal (scale =2), adapt_delta = 0.99) were used for Bayesian estimation of all treatment effect parameters and for the heterogeneity variance in random effects models, unless the model presented convergence issues. In these cases, informative priors were used and reported together with results in Appendix 4.[57, 58]

Model assessment and selection

Model selection between fixed and random effects was based on the Deviance Information Criterion (DIC), with a difference of 3-5 points considered meaningful.[59, 60] For models with similar DIC we selected the simplest model (lowest effective number of parameters) as this supports interpretability. The total residual deviance, as described in NICE DSU TSD 2,[56] was calculated, and compared to the number of datapoints as an overall assessment of goodness-of-fit.[56] Studies with high residual deviance were qualitatively assessed (e.g., for differences in line of therapy, disease severity, year of publication, concomitant medications).

Network meta-regression

NMA assumes that all effect modifiers are balanced across studies both within (homogeneity) and between (consistency) treatment comparisons. We had intended to assess the impact of effect modifiers using aggregate data network meta-regression, as described in NICE DSU TSD 3[61] for the outcomes ARR and disease progression. However, as there was little evidence of heterogeneity for ARR and CDP3, and insufficient studies for CDP6, meta-regression was not conducted. Instead, we conducted a sensitivity analysis restricted to studies judged at low risk of bias for ARR, the only outcome with sufficient studies for this to be considered appropriate.

Inconsistency testing

For any networks of evidence with closed loops of direct and indirect evidence we assessed consistency in the final by conducting a node-splitting analysis. Node-splitting models were fitted, where each comparison in the network was split into its direct and indirect components. For each node, we compared the estimates derived from direct and indirect evidence for comparisons against placebo, by calculating the difference in treatment effects and assessing whether the 95% credible intervals (CrIs) overlapped. We also examined the Bayesian p-values from the node-splitting models, which indicate whether there is evidence of inconsistency (i.e., significant differences between direct and indirect evidence).[62]

Model Implementation

Data preparation was conducted in the R programming language.[63] The NMA models were fitted in a Bayesian framework using the R package 'multinma'.[60, 64] Sufficient chains and Markov Chain Monte Carlo (MCMC) samples were used for burn-in and sampling. Convergence was assessed by visual inspection of the trace plots and the Brookes-Gelman-Rubin (BGR) Rhat statistic, which is reported for model parameters.[60]

Populations

We conducted our NMA on all feasible outcomes in the following populations:

1. HARRMS (or studies with at least 90% participants in this group)
2. Any RRMS, including studies with at least 90% of participants with RRMS.

A sensitivity analysis was conducted where a restricted NMA was created for population 2, including only interventions assessed in population 1.

Timepoints

Studies reported outcomes at multiple timepoints. We included all reported time points in the analysis, where studies reported outcomes at multiple time-points we selected the longest follow-up period. Where appropriate data were available, we used hazard ratios to account for differing follow-up periods across the included studies. We had intended to conduct a sensitivity analysis where we would have conducted separate analyses for 12, 24 and 36 months follow-up. However, there were insufficient data on time-points other than 24 months and so this analysis was not considered feasible.

Handling of multi-arm trials

Multi-arm trials were included in the network meta-analysis, and all relevant arms were included in the analyses. These studies were handled automatically using the multinma package in R, which adjusts for correlations within multi-arm studies.

Summary of results

Results were summarised as the mean of the posterior distribution of the treatment effect. The results of the NMA were presented in terms of cross tables with relative treatment effect estimates between all interventions of interest with 95% CrI for all outcomes presented. We also plotted data, including results from the node split models on forest plots to show effects of each intervention included in the network relative to placebo. All results are reported with 95% credible intervals (CrI). The 95% CrI were calculated as the lower 2.5th and upper 97.5th percentile of the MCMC samples. One of the advantages of NMA is that it allows for the ranking of interventions. Based on the results of the NMA, we calculated the probability of each treatment is ranked 1st best, 2nd best, etc. We also presented the mean ranking for each intervention together with 95% CrI, and league tables (RR of HR with 95% CrI) to show comparisons between each pair of included interventions.

The results of the NMA were also used to inform the economic model, as described in Section 6.5.1.

4.4 Protocol changes

The following changes were made to the protocol. These were either to clarify issues that were ambiguous in the original protocol or to focus the review to make this manageable within the resources and time available. Restrictions to outcomes were discussed with and approved by NICE.

4.4.1 Inclusion criteria:

Population: We clarified that RRMS was defined broadly to include studies of patients reported to have “relapsing MS”, and that we were only interested in studies in adults (>18 year olds).

Interventions: We restricted inclusion to studies that evaluated the interventions of interest at modes of administration and doses licensed for use in UK unless they were required to create a connected network.

Outcomes: Due to time and resource constraints, we restricted inclusion to studies that reported on at least one of the following outcomes:

- Relapse rate
- MRI measurements
- Disability progression
- Disease progression
- Adverse effects of treatment
- Health-related quality of life measured using EQ-5D or SF-36

This means that we did not consider the following outcomes:

- Severity of relapses
- Symptoms of multiple sclerosis (such as fatigue, cognition, and visual disturbance)

4.4.2 Literature searches

Rather than screening the existing TAs as a first step, we screened these after we had completed the data extraction for studies identified by bibliographic and non-bibliographic search methods. This was a logistical change to allow us to also determine whether there were any additional data reported in the TAs that were not available in reports of the studies. Additional data could then be included in the review.

4.4.3 Data extraction

We restricted data extraction to the outcomes listed above, focusing specifically on those listed in the methods section of the report. Data extraction was performed in Nested Knowledge instead of Access as initially proposed. We were not aware of this programme at the time the protocol was written – this allowed two reviewers to work remotely on the same database and provided greater efficiencies in the review process.

Due to time and resource constraints, we restricted data extraction and synthesis to the outcomes:

- Annualised Relapse Rate (ARR)
- Disease progression (CDP3 and CDP6)
- MRI outcomes (proportion of participants with Gd+ or new or enhancing T2 lesions)
- Adverse events (any AEs, serious AEs, grade 3-4 AEs, treatment related AEs and discontinuation due to AEs)
- Quality of life

4.4.4 Synthesis and network meta-analysis

Dichotomous data (proportion of participants with MRI lesion sand AE outcomes) were analysed as time to event outcomes, with HR and se(logHR) calculated as shown in 4.3.4. This was done because all outcomes were only expected to occur once per patient, and it allowed us to introduce follow-up time into our calculations.

We had planned to use network meta-regression to investigate heterogeneity in relapse rates and disease progression across studies. However this was not considered to be appropriate for ARR as there was little evidence of heterogeneity, and there were not enough data for other outcomes.

Consistency was evaluated using node splitting and plotting indirect and direct effect estimates against NMA results. Bayesian p-values were also considered. We did not find any inconsistencies, so a comparison of model fit with the Unrelated Mean Effects (UME) model was not done.

We removed the prediction of absolute outcomes from the NMA as absolute outcomes in data from the MS Registry analysis was available to inform the economic model.
We had intended to conduct a sensitivity analysis for the HARRMS population, where treatments that were disconnected would be included through an “any RRMS” study from population 2. Instead, we conducted a sensitivity analysis where a restricted NMA was created for the general RRMS population, including only interventions assessed in people with HARRMS. This restricted NMA in the general RRMS population was plotted together with results from the equivalent network in the HARRMS population for comparison. We considered that this would provide a better comparison of whether interventions are similarly effective in the RRMS and HARRMS populations.

5 Results of clinical effectiveness review

Our searches identified 3021 records of which 701 reports were considered potentially relevant after screening titles and abstracts and were retrieved for full text review. We identified two additional relevant studies – one that was published since the searches[65] but for which the trial registry entry was identified by the searches, and one abstract included in a previous systematic review. We were unable to locate a full report of this study and the abstract did not contain sufficient details to include the trial.[66] The flow of studies through the review process is shown in the PRISMA flow diagram in Figure 2.[48]

We included 42 studies (22, 409 participants) reported in 178 reports. This includes two sets of paired studies (OPERA I and OPERA II[67] and ASCLEPIOS I and II[68]) that were reported together in the same set of reports. Table 46 (Appendix 3) provides an overview of each included study,
Table 47 (Appendix 3) summarises reports related to each study and whether additional data were extracted from each report. Studies excluded at the full text assessment stage are summarised in Table 44 (Appendix 2), together with reasons for exclusion. The submissions from the manufacturers for the two drugs of interest for this appraisal (Biogen and Sandos) did not include any relevant studies that we had not identified in our searches – studies included in these submissions, review decision, and reasons for exclusion (where appropriate) are summarised in Table 42 and Table 43 (Appendix 3). We identified a further eight studies that appeared to meet inclusion criteria but are currently ongoing and so results are not yet available. These are summarised in Table 41 (Appendix 2) – interventions being evaluated include stem cell transplantation (4 studies), ocrelizumab, ofatumumab, interferon beta-1a, interferon beta-1b, glatiramer acetate and natalizumab (each in single studies) .

We only identified one small study ofatumumab - APOLITOS[69], and this was conducted in the very specific population of Japanese and Russian participants. We therefore expanded our inclusion criteria to include studies that compared ofatumumab to other interventions not specified in our original inclusion criteria. This led to the inclusion of an additional 2 studies: ASCLEOPIO I and II[68] that compared ofatumumab to teriflunomide. To create a connected network, we also included the OPTIMUM trial[70] that compared teriflunomide with ponesimod. These three studies are included in our total number of 42 included studies.

Two of the 42 studies included in our review – CARE-MS II[71] and MIST[72] - were restricted to participants with HARRMS. All other studies reported data for the full RRMS population. Six studies (CLARITY[73], FREEDOMS[74], FREEDOMS II[73], OPERA I and II[67], and TRANSFORMS)[75] also reported additional data for a subset of patients with HARRMS. There were no data on natalizumab or natalizumab biosimilar in people with HARRMS.

Table 5 provides an overview of the interventions evaluated by the included studies – different doses of the same interventions were considered as separate interventions. Twenty studies included a placebo control group, three of these also included an active comparator, and 22 studies included active comparators only. We identified only one study of AHSCT, the MIST study.[76] This study was conducted in patients with HARRMS and compared AHSCT to a DMT. Patients in the DMT group received a DMT of higher efficacy or

a different class to the intervention they had been taking at the time of randomisation, based on the judgement of the neurologist - this meant that individual patients received different DMTs.

Only four studies evaluated natalizumab or natalizumab biosimilar, the technologies of interest for this appraisal - ANTELOPE[76], AFFIRM[77], REVEAL[78] and Saida 2017[79]. AFFIRM and Saida 2017 compared natalizumab to placebo, REVEAL compared natalizumab to Fingolimod, and ANTELOPE compared natalizumab to natalizumab biosimilar. All studies of natalizumab evaluated intravenous administration; there were no studies that fulfilled our inclusion criteria of subcutaneous administration. Table 6 provides an overview of the four studies that evaluated natalizumab. All four studies used the McDonald criteria to diagnose MS and were industry funded. Saida 2017 was conducted in Japanese patients, REVEAL did not report on ethnicity but was conducted across 9 countries, and in AFFIRM and ANTELOPE most participants (94-100%) were white. AFFIRM had a follow-up duration of 24 months, follow-up duration was short (24-52 weeks) in the other three studies. A large proportion of patients in the Saida 2017 study had received previous DMT treatment (88%), and participants were required to have had at least one relapse at baseline, meaning participants were close to fulfilling our definition of HARRMS. Half of participants had received previous DMT treatment in REVEAL, while only 9% of those in AFFIRM had received treatment; information on previous treatment was not reported for ANTELOPE. All studies reported on relapse rates and AEs, and all but Saida 2017 reported in the proportion of participant with MRI lesions. AFFIRM was the only study to provide data on disease progression.

Figure 2 PRISMA Flow diagram

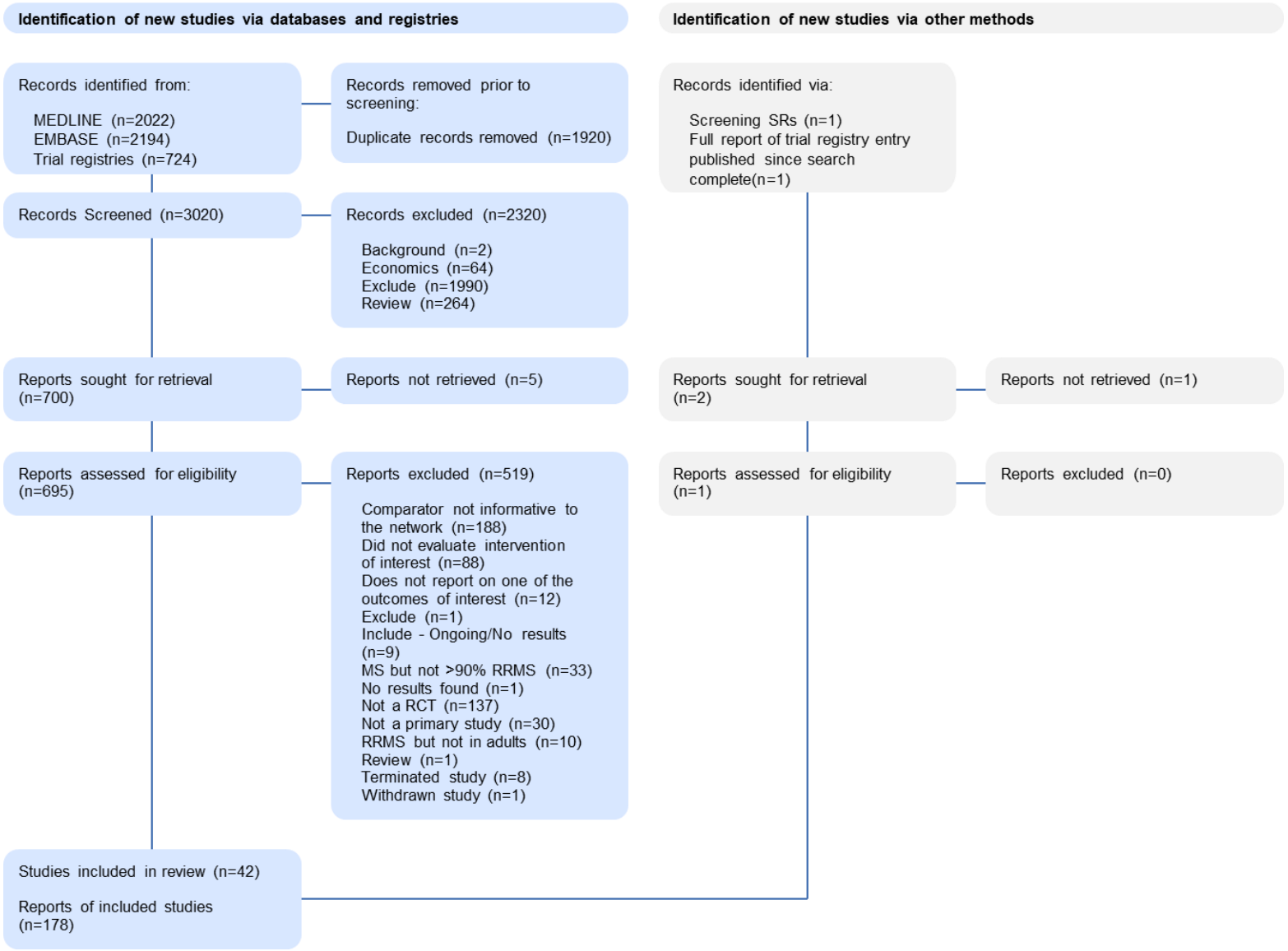


Table 5 Overview of interventions evaluated in each of the included studies

Study Name	Population	Intervention																	
		Placebo	Interferon beta 1a IM30	Interferon beta 1a SC44	Interferon beta 1a SC22	Interferon beta 1b SC250	Peginterferon beta 1a SC125	Glatiramer acetate SC20	Glatiramer acetate S420	Fingolimod O0.5	Ponesimod O20	Ocrelizumab IV600	Alemtuzumab IV12	Natalizumab IV300	Natalizumab biosimilar	Ofatumumab SC20	Cladribine O3.5	Teriflunomide O14	AHSCT
ADVANCE[80]	RRMS	x					x												
AFFIRM[77]	RRMS	x												x					
ANTELOPE[76]	RRMS													x	x				
APOLITOS[69]	RRMS	x														x			
ASCLEPIOS I[68]	RRMS															x		x	
ASCLEPIOS II[68]	RRMS															x		x	
ASSESS[81]	RRMS							x		x									
BEYOND[82]	RRMS					x		x											
Calabrese 2012[83]	RRMS	x		x				x											
CAMMS223[84]	RRMS			x									x						
CARE-MS I[85]	RRMS			x									x						
CARE-MS II[71]	HA			x									x						
CLARITY[86]	RRMS + HA		x														x		
CombiRx[87]	RRMS		x					x											
CONFIDENCE[88]	RRMS							x	x										
CONFIRM[89]	RRMS	x						x											
Copolymer 1 Multiple Sclerosis Study Group[90]	RRMS	x						x											
Etemedifar 2006[91]	RRMS		x	x		x													
European/ Canadian	RRMS	x						x											

Study Name	Population	Intervention																		
		Placebo	Interferon beta 1a IM30	Interferon beta 1a SC44	Interferon beta 1a SC22	Interferon beta 1b SC250	Peginterferon beta 1a SC125	Glatiramer acetate SC20	Glatiramer acetate S420	Fingolimod O0.5	Ponesimod O20	Ocrelizumab IV600	Alemtuzumab IV12	Natalizumab IV300	Natalizumab biosimilar	Ofatumumab SC20	Cladribine O3.5	Teriflunomide O14	AHSCT
glatiramer acetate study group[92]																			
EVIDENCE[93]	RRMS		x	x															
FREEDOMS[74]	RRMS + HA	x								x									
FREEDOMS II[73]	RRMS + HA	x								x									
GALA[94]	RRMS	x							x										
GATE[95]	RRMS	x						x											
GOLDEN[96]	RRMS					x				x									
IFNB Multiple Sclerosis Study Group[97]	RRMS	x				x													
IMPROVE[98]	RRMS	x		x															
INCOMIN[99]	RRMS		x			x													
Kappos 2011[100]	RRMS	x	x									x							
MIST[72]	HA																		x
OPERA I[67]	RRMS + HA			x								x							
OPERA II[67]	RRMS + HA			x								x							
OPTIMUM[70]	RRMS										x							x	
PEGINTEGRITY[65]	RRMS	x					x												
Ponesimod Phase II study Group[101]	RRMS	x									x								
PRISMS[102]	RRMS	x		x	x														
REGARD[103]	RRMS			x				x											
REVEAL[78]	RRMS									x				x					
Saida 2012[104]	RRMS	x								x									

Study Name	Population	Intervention																		
		Placebo	Interferon beta 1a IM30	Interferon beta 1a SC44	Interferon beta 1a SC22	Interferon beta 1b SC250	Peginterferon beta 1a SC125	Glatiramer acetate SC20	Glatiramer acetate S420	Fingolimod O0.5	Ponesimod O20	Ocrelizumab IV600	Alemtuzumab IV12	Natalizumab IV300	Natalizumab biosimilar	Ofatumumab SC20	Cladribine O3.5	Teriflunomide O14	AHSCT
Saida 2017[79]	RRMS	x												x						
The Multiple Sclerosis Collaborative Research Group	RRMS	x	x																	
TRANSFORMS[75]	RRMS + HA		x							x										

RRMS: Relapsing remitting MS; HA: highly active

Table 6 Overview of study details and baseline characteristics for studies that evaluated natalizumab or its biosimilar

Study Name	Interventions evaluated	Number enrolled	Duration (median follow-up)	Study Location	Age	% Female	Years from diagnosis	EDSS	Relapse rate	% treated	Outcomes reported
AFFIRM[77]	Natalizumab Placebo	943	2 years	99 sites in Europe, North America, and New Zealand	36.0	70	NR	2.3	1.5	9	ARR, CDP3, CDP6, MRI Gd+, MRI T2, any AEs, SAEs, AEs leading to treatment discontinuation
ANTELOPE[76]	Natalizumab Natalizumab biosimilar	265	48 weeks	48 sites in 7 countries	36.7	61	5.3	3.3	1.4	NR	ARR, MRI Gd+, MRI T2, any AEs, treatment related AEs, AEs leading to treatment discontinuation
REVEAL[78]	Natalizumab Fingolimod O0.5	111	52 weeks	43 sites in nine countries.	36.6	69	4.8	NR	1.9	50	ARR, MRI Gd+, MRI T2, SAEs, treatment related AEs, AEs leading to treatment discontinuation
Saida 2017[79]	Natalizumab Placebo	94	24 weeks	25 sites in Japan	36.4	70	5.5	2.2	2.0	88	ARR, any AEs, SAEs, AEs leading to treatment discontinuation

Table 7 Risk of bias for studies in the general RRMS population

Study	Outcome	Domain					Overall	Rationale
		1	2	3	4	5		
ADVANCE[80]	ARR; CDP; AE; QoL	Low	Low	Low	Low	Low	**Low**	No concerns for any domains
AFFIRM[77]	ARR; MRI	Low	Low	Low	Low	Low	**Low**	No concerns for any domains; protocol not available but ARR and MRI specified as outcomes in trial registry entry
	CDP					Some concerns	**Some concerns**	Outcome not specified in trial registry entry
	QoL			High		Low	**High**	Outcome data only available for 85% participants
ANTELOPE[76]	ARR; MRI; AE	Low	Low	Low	Low	Low	**Low**	No concerns for any domains
APOLITOS[69]	ARR; AE	Some concerns	Low	Low	Low	Low	**Some concerns**	Insufficient information on randomisation and allocation concealment; no evidence of baseline imbalance; protocol not available
ASCLEPIOS I[68]	ARR; CDP; AE	Low	Low	Low	Low	Low	**Low**	No concerns for any domains
ASCLEPIOS II[68]	ARR; CDP; AE	Low	Low	Low	Low	Low	**Low**	No concerns for any domains
ASSESS[81]	ARR; MRI; AE	Low	High	High	Low	Low	**High**	Patients and carers were aware of the treatment assignments; large proportion of withdrawals potentially related to outcomes; subset received MRI; all participants included in analysis, but details on ITT analysis lacking
BEYOND[82]	ARR; CDP; AE	Low	Low	Low	Low	Some concerns	**Some concerns**	Protocol not available
Calabrese 2012[83]	ARR	Some concerns	Some concerns	Low	Some concerns	Some concerns	**Some concerns**	Insufficient information on allocation concealment; no evidence of baseline imbalance; patients and carers were aware of the treatment assignments but no evidence of protocol deviations because of trial context; no information on blinding of outcome assessors; protocol not available
CAMMS223[84]	ARR; CDP	Some concerns	Some concerns	High	Low	Low	**High**	Insufficient information on allocation concealment; patients and carers aware of treatment assignment but deviations from intended intervention low; large proportion of missing data potentially related to outcome - all participants included in analysis but details on ITT analysis lacking
	AE			Low				Outcome data available for most participants
CARE-MS I[85]	ARR; CDP; MRI; AE; QoL	Some concerns	High	Low	Low	Low	**High**	Insufficient information on allocation concealment; patients and carers were aware of the treatment assignments

Study	Outcome	Domain					Overall	Rationale
		1	2	3	4	5		
CLARITY[86]	ARR; CDP; MRI; QoL	Low	Low	High	Low	Low	**High**	Over 10% of participants did not complete study & only subset of these had MRI data; missingness could depend on true value. Only 80% of participants had data for QoL
	AEs	Low	Low	Low	Low	Low	**Low**	Data available for all participants
CombiRx[87]	ARR; AE	Low	Low	Low	Low	Low	**Low**	No concerns for any domains
	MRI			Some concerns			**Some concerns**	MRI data only available for subset of patients, unclear how selected; no sensitivity analysis and missingness could depend on true value
CONFIDENCE[88]	AE	Some concerns	Low	Low	High	Some concerns	**High**	Insufficient information on randomisation and allocation concealments; outcome assessors unblinded; no protocol
CONFIRM[89]	ARR; CDP; QoL (except VAS)	Low	Low	Some concerns	Low	Low	**Some concerns**	Data missing for 20% of participants but sensitivity analysis suggest that this did not impact results; protocol not available
	AE; QoL (VAS)			Low			**Low**	AE data for all participants; QoL VAS for >90%
Copolymer 1 Multiple Sclerosis Study Group[90]	ARR; CDP; AE	Some concerns	Low	Low	Low	Some concerns	**Some concerns**	Insufficient information on allocation concealment; no evidence of baseline imbalance; protocol not available
Etemedifar 2006[91]	ARR	Some concerns	Some concerns	Low	Low	Some concerns	**Some concerns**	Insufficient information on allocation concealment; no evidence of baseline imbalance; patients and carers were aware of the treatment assignments but no evidence of protocol deviations because of trial context; protocol not available
European/ Canadian glatiramer acetate study group[92]	ARR; AE	Some concerns	Low	Low	Low	Low	**Some concerns**	Insufficient information on allocation concealment; no evidence of baseline imbalance
EVIDENCE[93]	ARR; CDP; MRI; AE	Low	Some concerns	Low	Low	Some concerns	**Some concerns**	Patients and carers were aware of the treatment assignments but no evidence of protocol deviations because of trial context; protocol not available
FREEDOMS[74]	ARR; CDP; AE	Low	Low	Low	Low	Low	**Low**	No concerns for any domains

Study	Outcome	Domain					Overall	Rationale
		1	2	3	4	5		
	MRI			Some concerns			**Some concerns**	MRI data only available for subset of patients, unclear how selected; no sensitivity analysis and missingness could depend on true value
FREEDOMS II[73]	ARR; CDP; MRI; QoL	Low	Low	High	Low	Low	**High**	Over 25% of participants did not complete study & only subset of these had MRI data; missingness could depend on true value
	AE			Low			**Low**	AE data available for all participants
GALA[94]	ARR; AE	Low	Low	Low	Low	Low	**Low**	No concerns for any domains
GATE[95]	ARR; MRI; AE	Low	Low	Low	Low	Low	**Low**	No concerns for any domains
GOLDEN[96]	ARR	Some concerns	High	High	Low	Some concerns	**High**	Insufficient information on allocation concealment; patients and carers were aware of the treatment assignments; large proportion of missing data potentially related to outcome; protocol not available
	AE			Low				Safety data available for all participants
IMPROVE[98]	ARR; MRI; AE	Some concerns	Some concerns	Low	Low	Some concerns	**Some concerns**	Insufficient information on allocation concealment; no evidence of baseline imbalance; patients and carers were aware of the treatment assignments but no evidence of protocol deviations because of trial context; protocol not available
INCOMIN[99]	ARR; CDP;	Low	High	Low	High	Some concerns	**High**	Patients and carers were aware of the treatment assignments; outcome assessors unblinded; no protocol available
	MRI		Some concerns				**High**	MRI outcome data only available for 80% of participants
IFNB Multiple Sclerosis Study Group[97]	ARR; AE	Some concerns	Low	Low	Low	Some concerns	**Some concerns**	Insufficient information on randomisation and allocation concealment; no evidence of baseline imbalance
Kappos 2011[100]		Low	Low	Low	Low	Low	**Low**	No concerns for any domains
Multiple Sclerosis Collaborative Research Group[105]	ARR; CDP; AE	Some concerns	Low	Low	Low	Low	**Some concerns**	Insufficient information on allocation concealment; no evidence of baseline imbalance
	MRI			Some concerns				MRI data available for 85% of participants

Study	Outcome	Domain					Overall	Rationale
		1	2	3	4	5		
OPERA I[67]	ARR; CDP; MRI; AE; QoL	Low	Low	Low	Low	Low	**Low**	No concerns for any domains
OPERA II[67]	ARR; CDP; MRI; AE; QoL	Low	Low	Low	Low	Low	**Low**	No concerns for any domains
OPTIMUM[70]	ARR; CDP; AE	Low	Low	Low	Low	Low	**Low**	No concerns for any domains
PEGINTEGRITY[65]	ARR; CDP;	Some concerns	High	High	Some concerns	Low	**High**	Insufficient information on allocation concealment and blinding of outcome assessors; patients and carers were aware of the treatment assignments; large proportion of missing data potentially related to outcome
	AE			Low				AE data available for >95% participants
Ponesimod Phase II study Group[101]	ARR; AE	Low	Low	Low	Low	Low	**Low**	No concerns for any domains
PRISMS[102]	ARR; CDP; MRI	Low	Low	Low	Low	Some concerns	**Some concerns**	Protocol not available
REGARD[103]	ARR; CDP; MRI; AE	Low	Low	Low	Low	Some concerns	**Some concerns**	Protocol not available.
REVEAL[78]	ARR; AE	Some concerns	Low	Low	Some concerns	Some concerns	**Some concerns**	Insufficient information on allocation concealment; no evidence of baseline imbalance; no information on blinding of outcome assessors; protocol not available
	MRI			Some concerns				MRI outcomes available for <90% of participants
Saida 2012[104]	ARR; AE	Low	Low	Low	Low	Low	**Low**	No concerns for any domains
	MRI			Some concerns			**Some concerns**	MRI outcome data only available for 88% of participants
Saida 2017[79]	ARR; AE	Low	Low	Low	Low	Low	**Low**	No concerns for any domains
TRANSFORMS[75]	ARR; CDP; AE	Low	Low	Low	Low	Low	**Low**	No concerns for any domains
	MRI			Some concerns				MRI data available for 85% participants

Domain 1: Risk of bias arising from the randomization process; Domain 2: Risk of bias due to deviations from the intended interventions; Domain 3: Risk of bias due to missing outcome data; Domain 4: Risk of bias in measurement of the outcome; Domain 5: Risk of bias in selection of the reported result

ARR: annualised relapse rate; CDP: confirmed disease progression; AE: adverse event; QoL: Quality of Life

5.1 General RRMS population

Forty studies (21,671 participants) reported data for a general RRMS population.

Table 48 (Appendix 3) provides a summary of the baseline characteristics of participants included in the RRMS studies. All studies were considered to be sufficiently similar for inclusion in the NMAs. AHSCT was the only intervention not evaluated in the general RRMS population – this was only evaluated in the HARRMS population. Four studies included a small proportion of participants that did not have RRMS – in ASCLEPIOS I and II 6% of participants had SPMS, in OPTIMUM 3% had SPMS, and in Saida 2012 2% had SPMS. Mean age ranged from 30 to 41 years (median 36.7 years), the proportion of female participants ranged from 31 to 91% (median 68%), baseline EDSS score from 1.0 to 3.5 (median 2.4), baseline annual relapse rate ranged from 0.7 to 2.4 (median 1.5), and mean disease duration at baseline ranged from 0.3 to 8 years (median 5.7 years). The proportion of participants who had received previous treatment with a DMT ranged from 0 to 91% (median 30%). The majority of participants were white (median 92%) although the proportion ranged from 0 to 100% - this is because one study (Saida 2007[79]) was conducted only in Japanese patients and the APOLITOS study[69] was conducted in Japan and Russia. Publication years spanned almost 30 years ranging from 1993 for the earliest study of interferon beta-1b to 2024, with a median of 2012.

5.1.1 Risk of bias

Table 7 provides a summary of the risk of bias assessment for studies in the RRMS population, stratified according to outcome. Results tables in Appendix 4, also include the overall risk of bias for each study for each outcome evaluated.

Domain 1: Risk of bias arising from the randomization process

No studies were judged as being at high risk of bias for the randomisation process, but 14 (35%) were judged at some concerns as they did not report sufficient information on randomisation and/or allocation concealment and there was no evidence of baseline imbalance between intervention groups. All other studies were judged as low risk of bias for this domain. Where studies reported multiple outcomes, risk of bias judgements were the same for all outcomes for this domain.

Domain 2: Risk of bias due to deviations from the intended interventions

Five studies (13%) were judged at high risk of bias due to deviations from the intended intervention – in these studies patients were aware of their treatment assignment and there was a differential rate of treatment discontinuation between the groups, which may have been associated with the outcome. Five studies (13%) were judged as some concerns for this domain as patients were aware of their treatment assignment but there was no evidence of deviations from the intended interventions. Where studies reported multiple outcomes, risk of bias judgements were the same for all outcomes for this domain.

Domain 3: Risk of bias due to missing outcome data

Six studies were judged at high risk of bias due to missing outcome data for the ARR outcome – these studies had a large proportion of missing outcome data (at least 10%) and this was considered to be potentially related to the outcome. Most of these studies did conduct an intention-to-treat (ITT) analysis based either on all randomised patients or on all

patients that received at least one dose of the intervention, but studies did not report sufficient details of how the ITT analysis was conducted. One study was judged as some concerns for this domain as although outcome data were missing for 20% of participants, sensitivity analysis suggested that this did not impact results.

Fourteen studies had different risk of bias judgements for the missing outcome domain for other outcomes reported. In eight studies, this was because MRI data were only available for <90% of participants, reasons for this were not reported and this was considered potentially related to the outcome. In six studies the missing outcome data domain was judged as some concerns for risk of bias for ARR, but at low risk of bias for safety data as outcome data were missing for ARR but were available for all, or almost all, participants for the adverse event outcomes.

Domain 4: Risk of bias in measurement of the outcome

Ony two studies were judged at high risk of bias for the measurement of the outcome domain – these specified that outcome assessors were unblinded. Three studies were judged at some concerns as it was unclear whether outcome assessors were blinded. Where studies reported multiple outcomes, risk of bias judgements were the same for all outcomes for this domain.

Domain 5: Risk of bias in selection of the reported result

No studies were judged as being at high risk of bias due to selective outcome reporting, but 14 (35%) were judged at some concerns as no protocol or trial registry entry was available, or the outcome was not specified in the trial registry entry. In the AFFIRM study, only two of the reported outcomes were specified in the trial registry entry – ARR and MRI. The study was therefore judged at low risk of selective outcome reporting for these outcomes but as some concerns for the other outcomes reported – disease progression and quality of life (QoL).

5.1.2 Annualised Relapse Rate (ARR)

All but one (CONFIDENCE[88]) of the 40 studies that reported results for the general RRMS population reported data on ARR and data were available for all interventions evaluated in the general RRMS population. Estimates of ARR for each study arm are summarised in Table 52 (Appendix 3). Studies reported ARR at between 4 and 36 months follow-up, with a median of 24 months follow-up. Included studies defined a "relapse" in different ways. Relapse definitions, broken down into definition components, are summarised in Table 50 (Appendix 3). Relapses were generally defined in terms of:

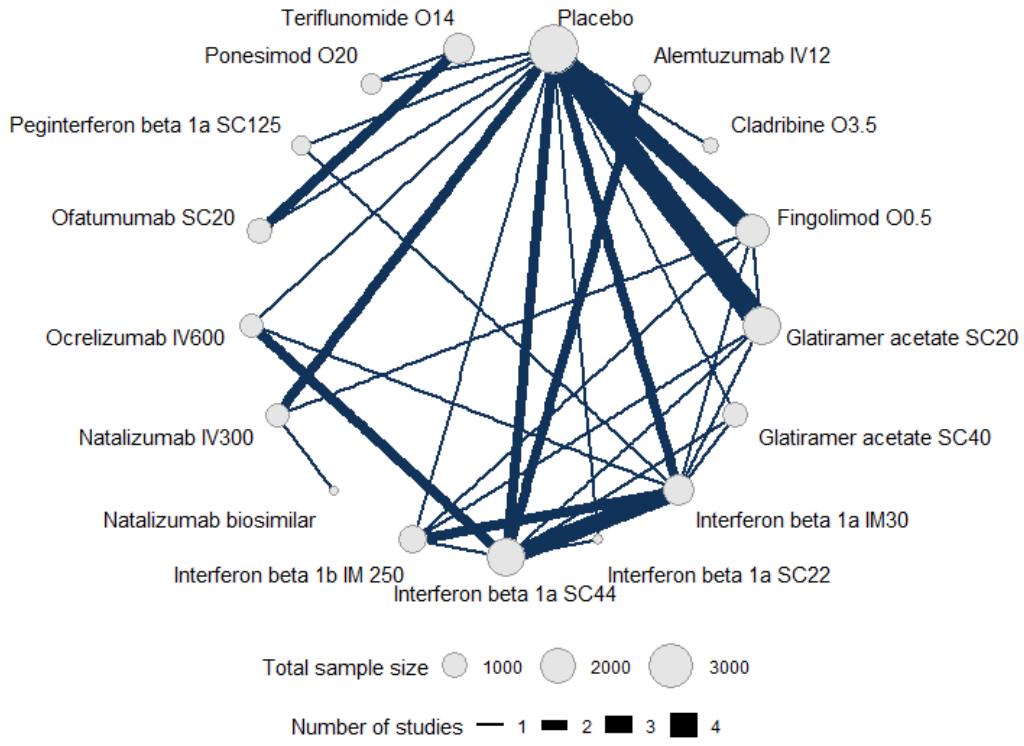
- *Symptoms*: combinations of new, recurrent or worsening of existing symptoms
- *Symptom duration*: at least 24 or 48 hours
- *Exclusion of specific clinical features*: fever, infection, heat intolerance, adverse reaction to medication
- *Neurological examination*: some studies specified that new objective neurologic findings were required, others were more specific specifying an EDSS increase $\geqslant$0.5 points, or increase $\geqslant$1 on two functional scores or $\geqslant$2 on one
- *Previous period of stability* – where required this was always a minimum of 30 days

- *Verification* – some studies specified that verification was required by a specific examiner, and some that this had to be within 7 days of notification of the potential relapse

Our clinical advisors suggested that these definitions were sufficiently similar for it to be appropriate to combine results across studies. For ARR, 17 (44%) studies were at low risk of bias, 15 (38%) had some concerns regarding risk of bias, and 7 (18%) were at high risk of bias.

The 39 studies (2,718 participants) created a connected network for 17 interventions of interest for this appraisal. The network geometry for this analysis is shown in Figure 3, displaying the treatment nodes and connections, with line thickness representing the number of studies for each comparison and node size the number of patients on each treatment. The placebo group served as the reference group throughout. Natalizumab biosimilar was only directly compared with natalizumab. Natalizumab was also directly compared to placebo and fingolimod and so could be compared to other treatments via these nodes.

Figure 3 Network plot for NMA for ARR



The DIC (77.7 vs 79.9)and residual deviance was also very similar for both fixed and random effects (49.8 vs 49.9 on 55 data points) (Table 62) were both similar for the fixed and random effects models, and indicated good fit for both models with limited heterogeneity in treatment effects across studies. This was confirmed by the heterogeneity standard deviation estimated by the random effects model (tau of 0.05, 95% CrI (0.002, 0.14), Table 62) being very low compared to the average treatment effect on the log rate ratio scale (-0.59 in Table 62). We therefore present results for the fixed effect models for this outcome.

Figure 28 (Appendix 5) shows how well each study fits the NMA model. The fixed effects model had a good fit to the data from most studies included in the network, with the exception of the REVEAL and GOLDEN studies, which also had high residual deviance under random effects. REVEAL compared natalizumab with fingolimod and GOLDEN compared fingolimod with interferon beta 1b. Both were multi-centre international studies and there were no clear differences between these two studies and other studies included in the network in terms of study design, outcome definition, or participant characteristics.

Figure 4 shows the Rate ratio (RR) and 95% credible intervals (CrI) for comparison of each intervention included in the network with placebo under the selected fixed effects model, stratified to show estimates from direct and indirect evidence and the overall NMA estimate. Comparison of estimates derived from direct and indirect evidence were similar. Most interventions were associated with a greater reduction (i.e., RR<1 AND 95% CrI excluding 1.00) in the risk of relapses compared to placebo. The exceptions were Teriflunomide and Ponesimod where the risk was similar to placebo. Results were very similar for both random and fixed effects models (Table 62 in Appendix 5). The ranking of interventions and the probability that each intervention would be ranked first is shown in Table 8, with Table 64 (Appendix 5) showing the probability that each intervention will rank in a specific position. Alemtuzumab had the highest mean ranking (1.4, 95 % CrI 1, 3) and the greatest probability of ranking first (72%) followed by natalizumab (2.3, 95 % CrI 1, 4; 17%). There was greater uncertainty for natalizumab biosimilar which had a 5% probability of ranking first but a mean ranking of 6.6 (95% CrI 1, 15). The different interferon and glatiramer acetate interventions were ranked similarly to each other and as less effective than most of the newer drugs. The exception to this were ponesimod and teriflunomide. Ponesimod had similar efficacy to the interferon and glatiramer acetate interventions, whilst teriflunomide was similar to placebo. Table 63 (Appendix 4) shows the RR (95% CrI) for each intervention pair comparison evaluated in the NMA. This shows that the RR (95% CrI) for natalizumab compared to natalizumab biosimilar, the key comparison for this appraisal, was 0.65 (0.34, 1.26), suggesting no difference between the ARR for these two interventions.

Figure 4 Forest plot of annualised relapse rate (ARR) ratios and 95% credible intervals (fixed effects NMA; RRMS population)

Blue lines indicate result from the NMA, green lines indicate results from direct evidence and purple lines from indirect evidence. P-values relate to comparisons between direct and indirect evidence. Note that the indirect evidence lines are only included if there is also direct evidence.

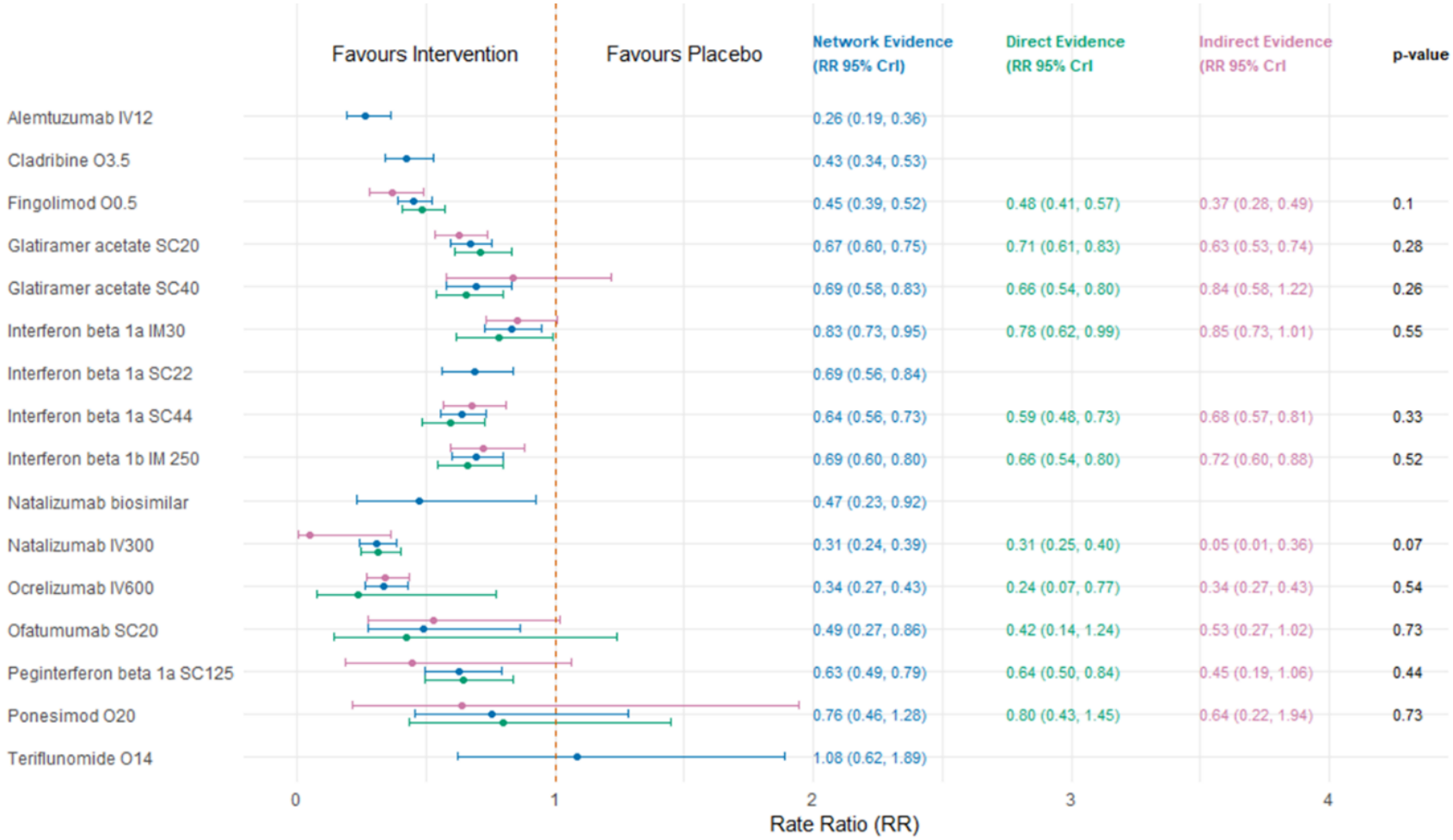


Figure 5 Forest plot of hazard ratios (HR) and 95% credible intervals for time to CDP3 (fixed effects NMA; RRMS population)

Blue lines indicate result from the NMA, green lines indicate results from direct evidence and purple lines from indirect evidence. P-values relate to comparisons between direct and indirect evidence. Note that the indirect evidence lines are only included if there is also direct evidence.

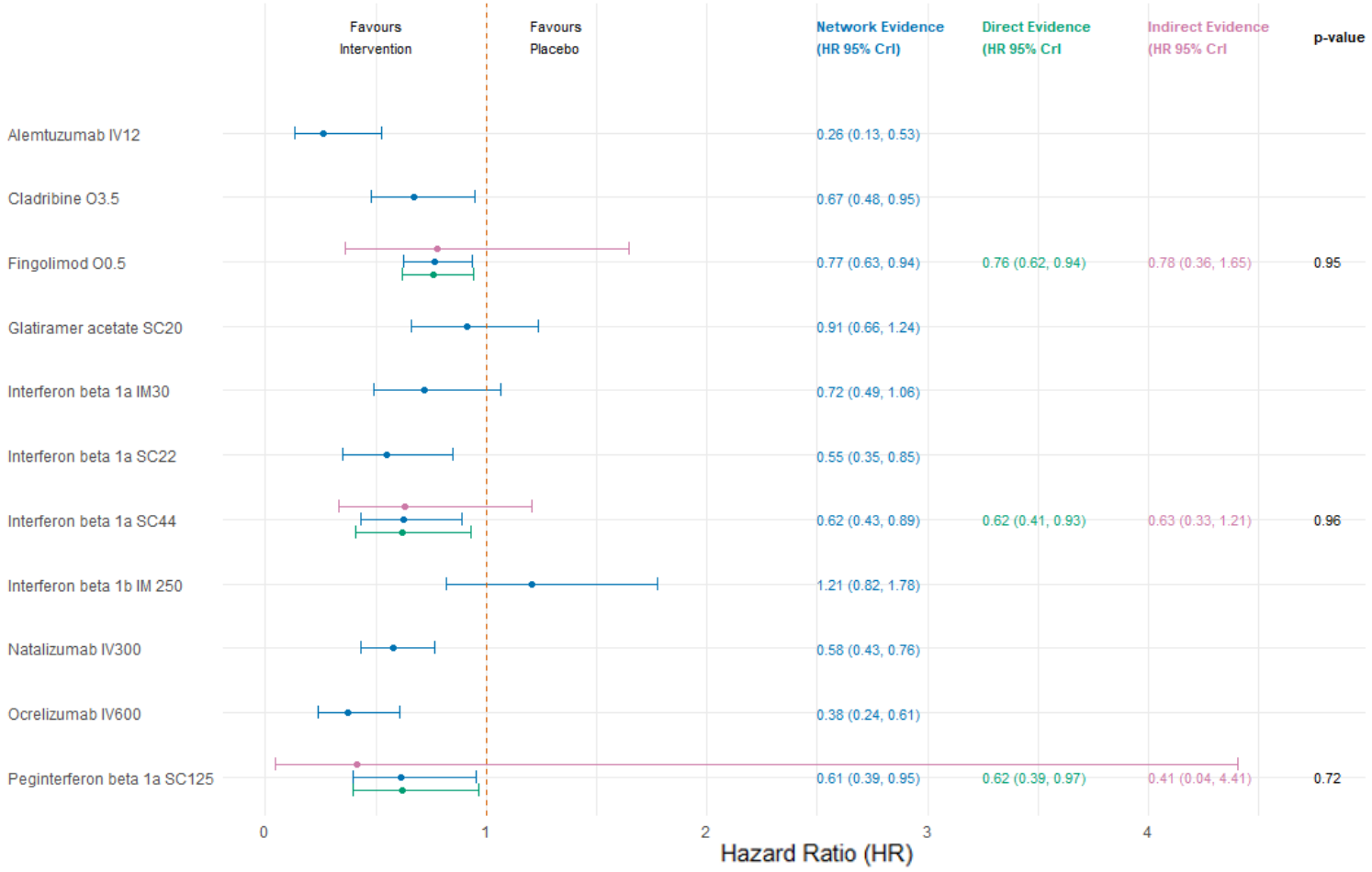


Figure 6 Forest plot of hazard ratios (HR) and 95% credible intervals from fixed effects NMA for time to CDP6 (fixed effects NMA; RRMS population).
Green lines indicate results from direct evidence and purple lines from indirect evidence.

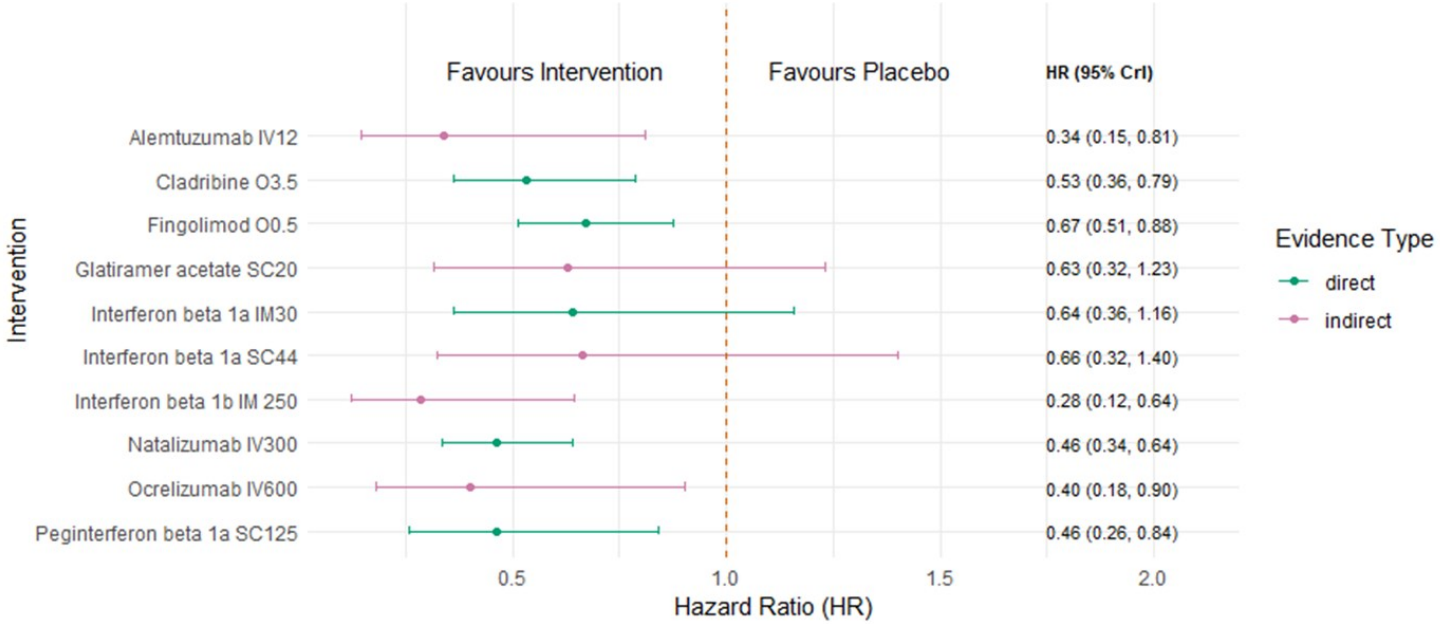


Figure 7 Forest plot of hazard ratios (HR) and 95% credible intervals for time to developing at least one Gd+ MRI lesion (fixed effects NMA; RRMS population)

Blue lines indicate result from the NMA, green lines indicate results from direct evidence and purple lines from indirect evidence. P-values relate to comparisons between direct and indirect evidence. Note that the indirect evidence lines are only included if there is also direct evidence.

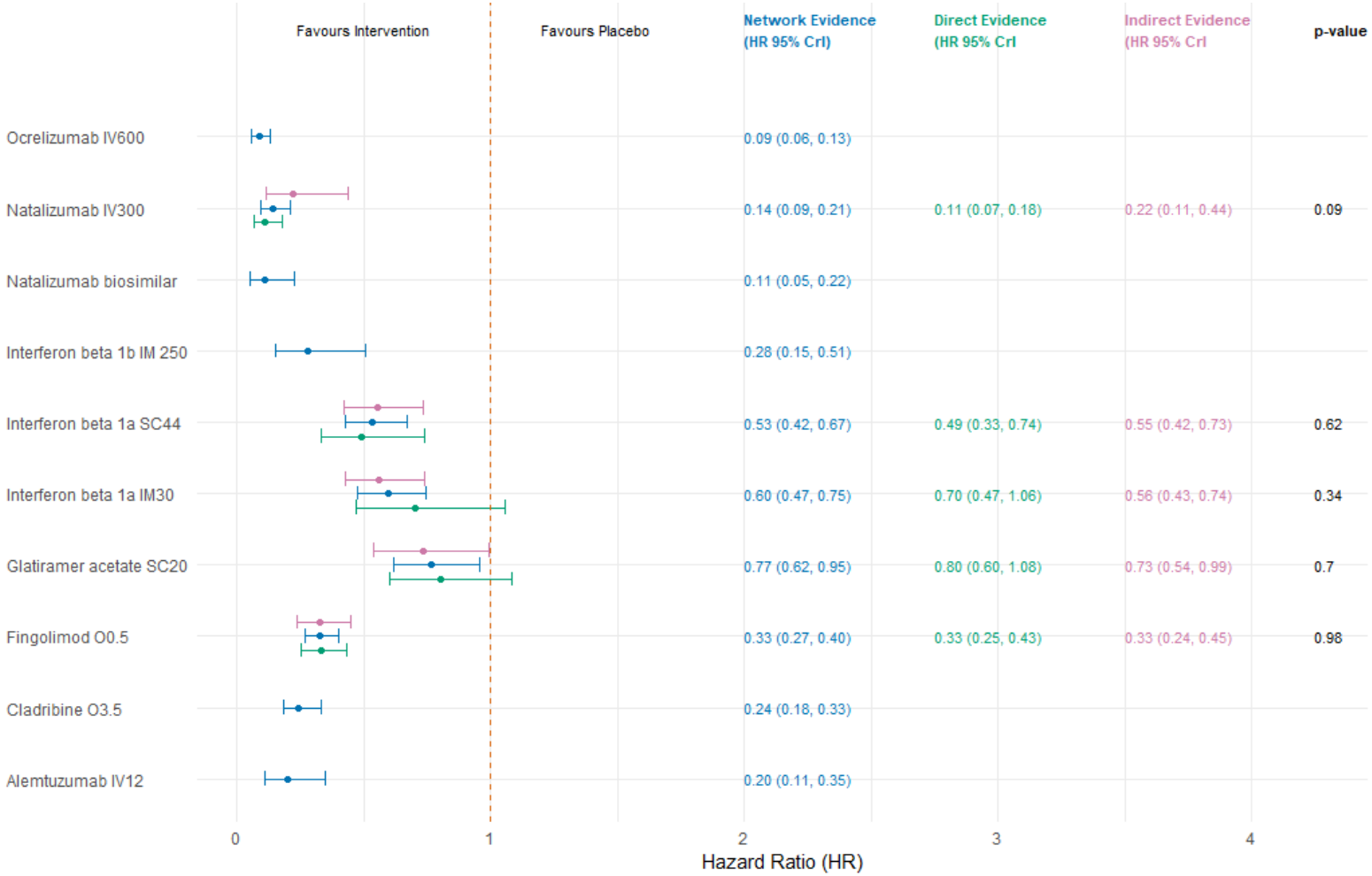


Figure 8 Forest plot of hazard ratios (HR) and 95% credible intervals for time to developing at least one new or enlarging T2 weighted MRI lesions (fixed effects NMA; RRMS population).

Blue lines indicate result from the NMA, green lines indicate results from direct evidence and purple lines from indirect evidence. P-values relate to comparisons between direct and indirect evidence. Note that the indirect evidence lines are only included if there is also direct evidence.

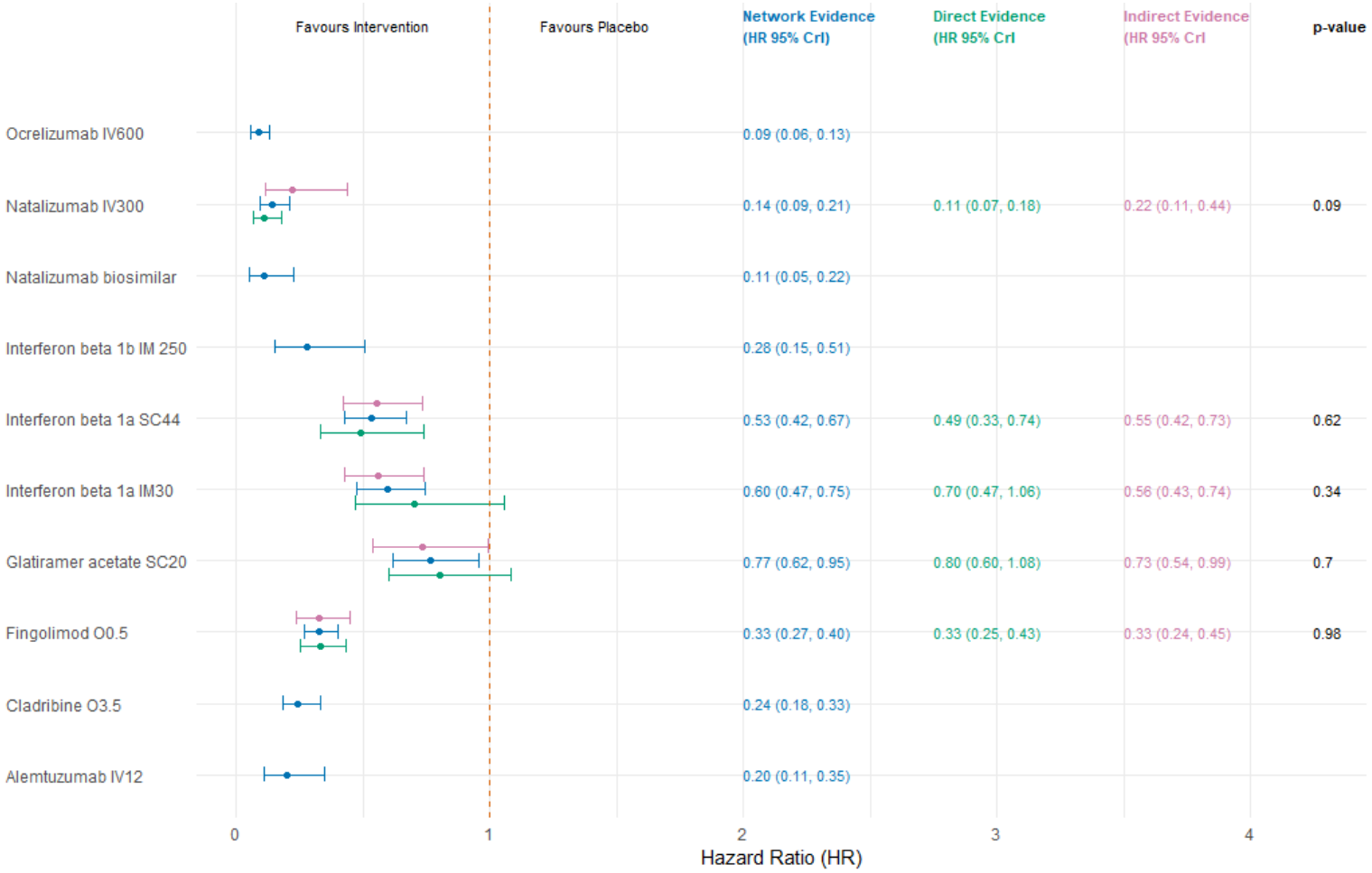


Table 8 Mean ranking of interventions and probability that each intervention would be ranked first from NMAs for each of the outcomes evaluated

Intervention	ARR		CDP3		CDP6		MRI: Gd+		MRI: T2		ARR (highly active)	
	Mean rank (95% CrI)	Pr(best) (%)	Mean rank (95% CrI)	Pr(best) (%)	Mean rank (95% CrI)	Pr(best) (%)	Mean rank (95% CrI)	Pr(best) (%)	Mean rank (95% CrI)	Pr(best) (%)	Mean rank (95% CrI)	Pr(best) (%)
Alemtuzumab IV12	1.4 (1, 3)	72	1.2 (1, 3)	83	2.7 (1,7)	26	4.2 (2, 7)	0	6.0 (3, 9)	3	3.8 (2, 5)	1
Natalizumab IV300	2.3 (1, 4)	17	4.8 (2, 9)	0	4.6 (1, 9)	5	2.9 (2, 4)	1	3.5 (1, 6)	4	1.8 (1, 5)	53
Natalizumab biosimilar	6.6 (1, 15)	5	NA	NA	NA	NA	2.1 (1, 4)	30	3.0 (1, 7)	31	NA	NA
Ocrelizumab IV600	3.1 (1, 5)	4	2.1 (1, 4)	14	3.8 (1, 8)	5	1.4 (1, 3)	68	2.2 (1, 5)	30	1.8 (1, 5)	44
Ofatumumab SC20	6.6 (2, 14)	2	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Cladribine O3.5	5.0 (3, 7)	0	6.5 (3, 10)	0	6.0 (2, 10)	0	5.1 (4, 7)	0	4.2 (1, 7)	0	4.1 (2, 6)	2
Fingolimod O0.5	5.5 (4, 7)	0	8.1 (5, 10)	0	8.1 (4, 10)	0	6.6 (5, 7)	0	6.4 (5, 8)	0	3.7 (2, 5)	0
Peginterferon beta 1a SC125	9.3 (6, 14)	0	5.5 (2, 10)	1	4.8 (1, 10)	10	NA	NA	8.2 (7, 10)	0	NA	NA
Interferon beta 1a SC44	9.4 (7, 13)	0	5.6 (3, 9)	0	8.1 (4, 11)	0	8.1 (8, 9)	0	NA	NA	6.5 (5, 7)	0
Interferon beta 1a SC22	11.2 (7, 15)	0	4.5 (2, 9)	2	NA	NA	NA	NA	10.6 (8, 12)	0		
Interferon beta 1a IM30	14.6 (13,16)	0	7.4 (3, 11)	0	7.7 (4, 11)	0	8.9 (8, 9)	0	9.2 (7, 11)	0		
Glatiramer acetate SC20	10.7 (8, 14)	0	9.6 (6, 11)	0	7.5 (4, 11)	0	10.0 (10, 10)	0	NA	NA	NA	NA
Glatiramer acetate SC40	11.3 (7, 15)	0	NA	NA	NA	NA	NA	NA	9.8 (8, 11)	0	NA	NA
Interferon beta 1b IM 250	11.4 (8, 15)	0	11.7 (10, 12)	0	2.0 (1, 6)	54	5.7 (3, 7)	0	3.1 (1, 8)	32	NA	NA
Ponesimod O20	12.3 (6, 16)	0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Teriflunomide O14	16.1 (10, 17)	0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Placebo	16.2 (15, 17)	0	10.8 (10, 12)	0	10.7 (8, 11)	0	11.0 (11, 11)	0	11.8 (11, 12)	0	6.4 (6, 7)	0

Sensitivity analysis for ARR

We had intended to conduct a meta-regression to investigate potential reasons for heterogeneity. However, as heterogeneity was low and covariates were broadly similar across groups this was not appropriate. Instead, we conducted a sensitivity analysis restricted to studies judged at low risk of bias. This analysis included 17 studies and created a connected network (Figure 29, Appendix 5), although data were not available for the following interventions: alemtuzumab, cladribine, interferon beta 1a (SC22), or interferon beta 1b. Estimates of RR for the interventions for which data were available were very similar to those obtained for the full set of studies, suggesting that risk of bias in these studies did not have a substantial impact on results. We investigated whether it was possible to carry out analyses separately for studies that reported data for 6, 12 and 24 month follow-up, but there were insufficient data and networks did not connect for follow-up of less than 24 months; the network for 24 months was almost the same as that for all studies combined.

5.1.3 Disease Progression

Only 23 of the 40 studies that reported results for the general RRMS population reported data on disease progression – 12 studies reported both CDP3 and CDP6, six studies reported CDP3 only and five reported CDP6 only. Estimates of CDP for each study arm are summarised in Table 52 (Appendix 4). Studies reported disease progression at between 6 and 24 months follow-up, with a median of 24 months follow-up. Included studies defined disease progression in different ways. Disease progression definitions, broken down into definition components, are also summarised in Table 52 (Appendix 4). All studies defined criteria for disease progression based on increase in EDSS scores and baseline EDSS scores – some simply specified an increase of at least one point regardless of baseline EDSS, others specified an increase of at least 1.5 points in those with a baseline EDSS score of 0 with an increase of at least one point in those with an EDSS score of at least one, and some specified an increase in EDSS score of 0.5 points in those with higher baseline EDSS scores (most commonly a baseline EDSS of more than 5 but in some this was more than 4.5 or 5.5). Our clinical advisors suggested that these definitions were sufficiently similar for it to be appropriate to combine results across studies.

Studies reporting data on CDP3 and CDP6 did not create a completely connected network for either outcome – for both outcomes, teriflunomide, ponesimod and ofatumumab did not connect to the network. We were therefore unable to include these interventions in the NMA. Studies of natalizumab biosimilar and glatiramer acetate SC40 did not report on disease progression and so these interventions were also excluded from the networks for CDP3 and CDP6.

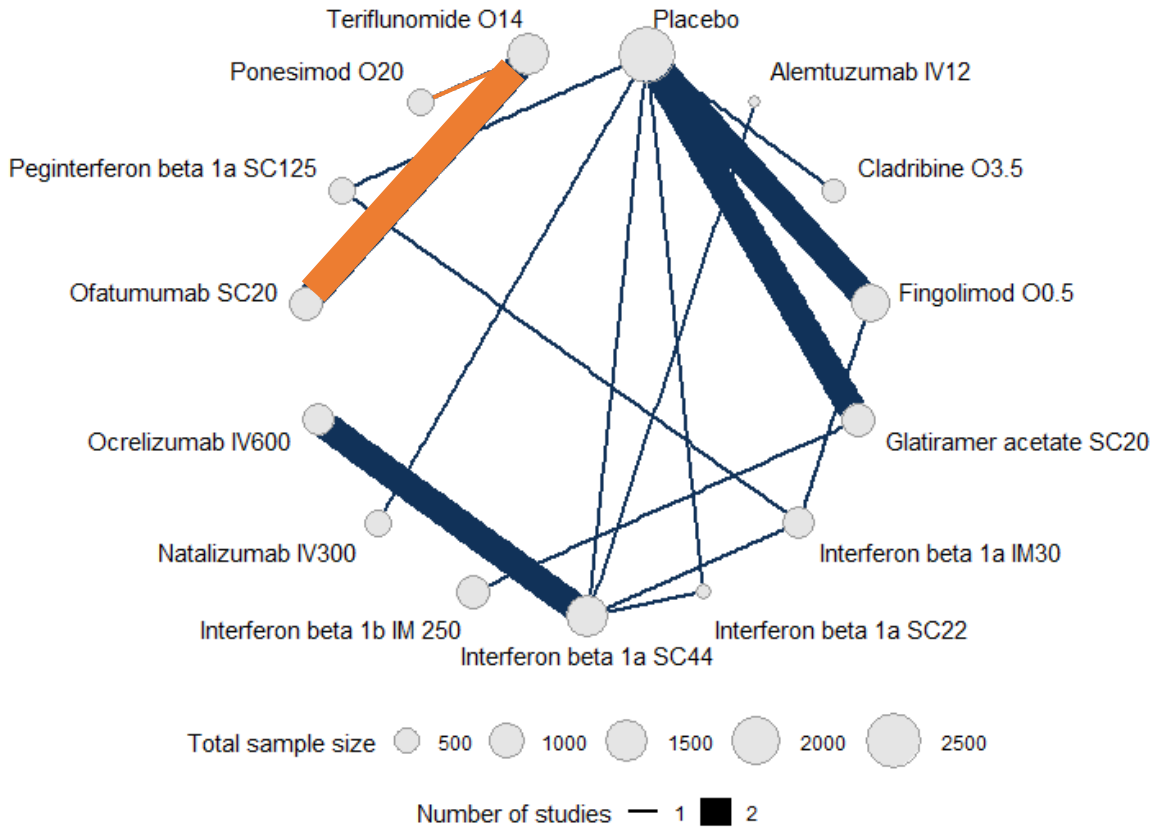
Of the 20 studies that were included in the NMAs for CDP3 and CDP6, six studies were judged at low risk of bias, nine at some concerns regarding risk of bias and five at high risk of bias.

CDP3

Following exclusion of the three studies that did not connect to the network (OPTIMUM, ASCLEPIOS I and ASCLEPIOS II), the remaining 15 studies (10, 824 participants) created a connected network for 11 interventions. The network geometry for this analysis is shown in

Figure 9, displaying the treatment nodes and connections, with line thickness representing the number of studies for each comparison and node size the number of patients on each treatment. The placebo group served as the reference group throughout.

Figure 9 Network plot of CDP3 NMA including disconnected treatments (shown with orange lines)



The DIC for the fixed effects model was slightly lower than for the random effects model (22.8 vs 25.1), suggesting that this model gives a better trade off between fit and complexity for the dataset (Table 67 in Appendix 3). The residual deviance was also lower for the fixed effects model than for the random effects model (11.8 vs 12.8 on 16 data points) indicating better fit for the fixed effects model. The DIC and residual deviance together indicate limited heterogeneity in treatment effects across studies. This was confirmed by the heterogeneity standard deviation estimated by the random effects model (tau (95% CrI) of 0.14 (0.005, 0.50), Table 67) being low compared to the average treatment effect on the log rate ratio scale (-0.48). We therefore present results for the fixed effect models for this outcome.

Figure 30 (Appendix 5) shows how well each study fits the NMA model. Both random and fixed effects model had a good fit to the data from all studies included in the network.

Figure 5 shows the HR and 95% credible intervals (CrI) for comparison of each intervention included in the network with placebo under the selected fixed effects model, stratified to show estimates from direct and indirect evidence and the overall NMA estimate. Comparison of estimates derived from direct and indirect evidence were similar. Alemtuzumab, ocrelizumab, natalizumab, fingolimod, cladribine and interferon beta 1a (SC22 and SC44) were associated with a greater reduction (i.e., HR<1 AND 95% CrI excluding 1.00) in the risk of CDP3 compared to placebo. There was little evidence to suggest a difference in the risk of CDP3 between those treated with glatiramer acetate or other interferon beta interventions and placebo. Results were very similar for both random and fixed effects models (Table 67 in Appendix 5). The ranking of interventions and the probability that each intervention would be ranked first is shown in Table 8 with Table 64 (Appendix 5) showing the probability that each intervention will rank in a specific position. Alemtuzumab had the highest mean ranking (1.2, 95 % CrI 1, 3) and the greatest probability of ranking first (83%) followed by ocrelizumab (2.1, 95 % CrI 1, 4; 14%). All other interventions in the network, including natalizumab, had a <5% probability of ranking first. Table 68 (Appendix 4) shows the HR (95% CrI) for each intervention pair comparison evaluated in the NMA.

Sensitivity analysis for CDP3

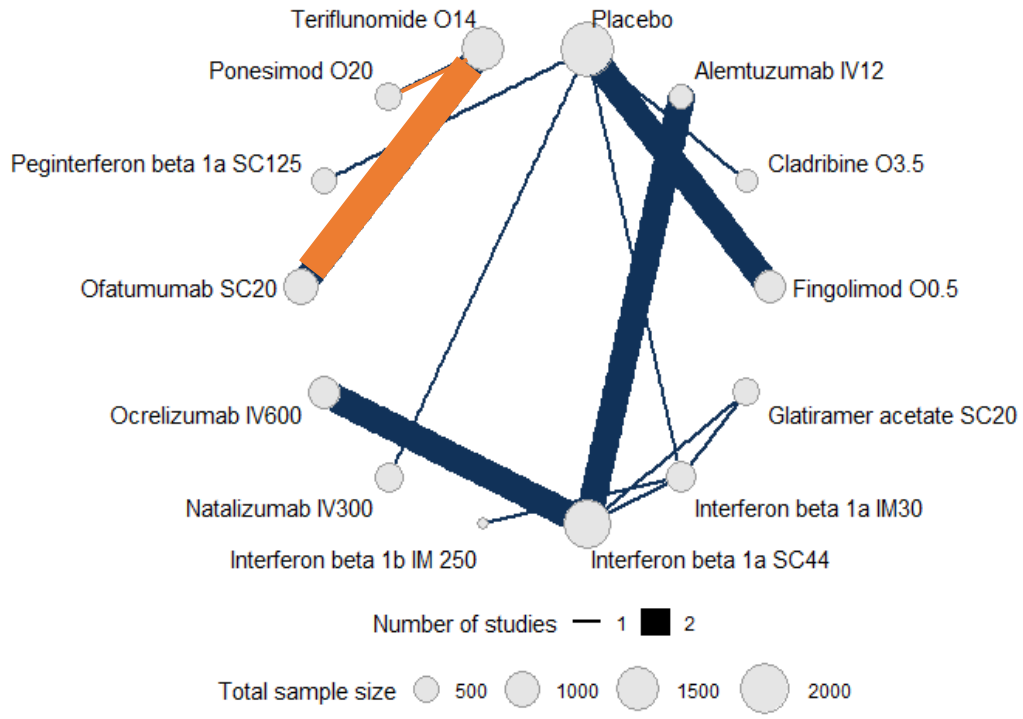
We ran a sensitivity analysis for CDP3 excluding studies with a follow up time of less than 24 months. Only five interventions were included in the network (natalizumab, cladribine, fingolimod, glatiramer and interferon beta 1b)((Figure 31 in Appendix 5), Effect estimates and rankings for the remaining interventions were similar to those for the primary analysis

Table 74 Comparison of results from fixed and random effects, mean ranking of interventions and probability that each intervention would be ranked 1st - NMA for CDP6 – Sensitivity analysis including studies with a follow-up ≥24 months (RRMS population.

CDP6

In addition to studies of natalizumab biosimilar and glatiramer acetate SC40 not reporting any data on disease progression, the studies of interferon beta 1a SC22 did not report on CDP6 and so this intervention was also excluded from the CDP6 network. The remaining 14 studies (n=9,006) created a connected network for the remaining 10 interventions of interest for this appraisal. The network geometry for this analysis is shown in Figure 10, displaying the treatment nodes and connections, with line thickness representing the number of studies for each comparison and node size the number of patients on each treatment. The placebo group served as the reference group throughout.

Figure 10 Network plot of CDP6 NMA including disconnected treatments (shown with orange lines)



The DIC for the random and fixed effects models were very similar (27.7 vs 28.0) (Table 71). The residual deviance was close to the number of data points for both studies (14.9 vs 18.0 on 14 data points) indicating a good fit for both models. The DIC and residual deviance together indicate limited heterogeneity in treatment effects across studies. The heterogeneity standard deviation estimated by the random effects model (tau (95% CrI) of 0.36 (0.02, 1.09) in Table 67) suggested moderate heterogeneity. Figure 32 (Appendix 5) shows how well each study fits the NMA model. The fixed effects model had a good fit to the data from all studies included in the network. We therefore present results for the fixed effect model for this outcome.

Figure 6 shows the HR and 95% credible intervals (CrI) for comparison of each intervention included in the network with placebo under the selected fixed effects model. Note that for this analysis there were no interventions for which both direct and indirect evidence were available – the plot shows which estimates were derived from each type of evidence. alemtuzumab, cladribine, fingolimod, interferon beta 1b, natalizumab, ocrelizumab, peginterferon beta 1a SC125 were associated with a lower risk of CDP6 than placebo. Results were similar for both random and fixed effects models (Table 71 in Appendix 5), although credible intervals were wider for the random effects model. There was considerable uncertainty in the ranking of interventions and the probability that each intervention would be ranked first (Table 8 and Table 78 (Appendix 5)).
Table 77 (Appendix 4) shows the HR (95% CrI) for each intervention pair comparison evaluated in the NMA.

Sensitivity analysis for CDP6

We ran a sensitivity analysis excluding studies with less than 24 months of follow-up. There were no studies reporting CDP6 for peginterferon beta 1a SC 125, so this intervention was excluded from the network (Figure 33 in Appendix 5). In this analysis, only cladribine, fingolimod, interferon beta 1b, and natalizumab showed evidence of a lower risk of CDP6 than placebo (

Table 74). There was also marked uncertainty in the ranking of interventions and the probability that each intervention would be ranked first.

INCOMIN[99] has been regarded as an outlier in previous publications due to inconsistencies in results for CDP3 and CDP6.[33, 41, 106, 107] We therefore conducted a sensitivity analysis excluding this study from the network. This resulted in interferon beta 1b being excluded from the network but results for other interventions were consistent with the primary analysis that included the INCOMIN trial (Figure 34 Network plot for NMA for CDP6 – excluding INCOMIN

Table 75 Comparison of results from fixed and random effects, mean ranking of interventions and probability that each intervention would be ranked 1st - NMA for CDP6 – Sensitivity analysis excluding INCOMIN (RRMS population)

CDP3/6 combined

We conducted a sensitivity analysis where we included the six studies that only reported CDP3 in the analysis for CDP6 to maximise the number of studies that contributed to this analysis. We included 20 studies (n=12,998) evaluating 11 interventions in this analysis. The network geometry for this analysis is the same as for the CDP3 analysis as this combined analysis allowed us to include interferon beta 1a SC22 which was not included in the CDP6 analysis (Figure 9). Results were very similar to those obtained for CDP6 alone (Appendix 5), although with narrower credible intervals. Results for CDP3 and CDP6 for INCOMIN were inconsistent, and this is reflected on a residual deviance well above 1 in Figure 35 Model fit for CDP3 and CDP6 combined assessed by individual study residual deviance (random effects analysis; RRMS population) Therefore, results for CDP6 for this study should be interpreted with caution.

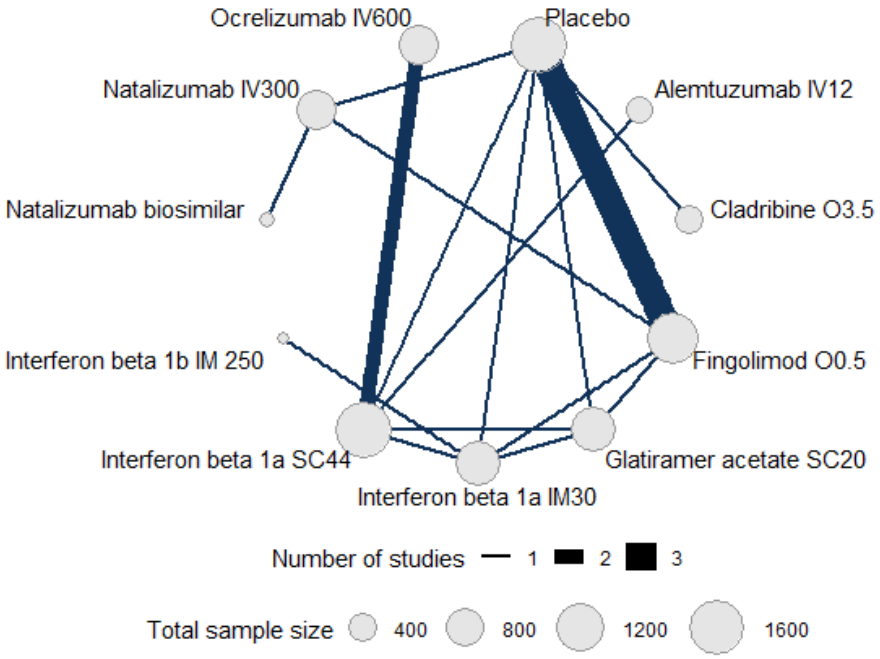
5.1.4 MRI Outcomes

Twenty studies reported data on at least one of the two MRI outcomes of interest for this appraisal: the proportion of patients with gadolinium enhancing (Gd+) or new or enlarging T2 lesions. All but one of these (PRISMS) reported data on Gd+ lesions, and all but three (CombiRx, GATE and Multiple Sclerosis Collaborative Research Group) reported data on T2 lesions. For Gd+ lesions, most studies reported on the proportion of patients with "any" Gd+ lesions, some reported only on new lesions. Studies reported MRI outcomes at between 4 and 24 months follow-up, with a median of 24 months. There were no data on MRI outcomes of interest for studies of the following interventions and so these were not able to be included in the NMAs for these outcomes: ofatumumab, glatiramer acetate (SC40), ponesimod, teriflunomide, and peginterferon beta 1a. Data for interferon beta 1a (SC22) were only available for T2 lesions and so it was only included for this outcome. Natalizumab biosimilar was only directly compared with natalizumab. Natalizumab was also directly compared to placebo and fingolimod and so could be compared to other treatments via these nodes.

Gadolinium (Gd+) enhancing lesions

Nineteen studies (9, 471 participants) reported data on Gd+ lesions and created a connected network for 11 interventions of interest for this appraisal (Figure 11). The placebo group served as the reference group throughout.

Figure 11 Network plot for NMA for proportion of participants with Gd+ lesions



The DIC (27.9 vs 28.5) and residual deviance (17.8 vs 16.5 on 19 data points) were similar for both fixed and random effects models and indicated good fit for both models with limited heterogeneity (Table 79). This was confirmed by the heterogeneity standard deviation estimated by the random effects model (tau (95% CrI) of 0.11 (0.006, 0.32) in Table 79). We therefore present results for the fixed effect models for this outcome. Figure 28 (Appendix 5) shows how well each study fits the NMA model. The fixed effects model had a good fit to the data from all studies included in the network.

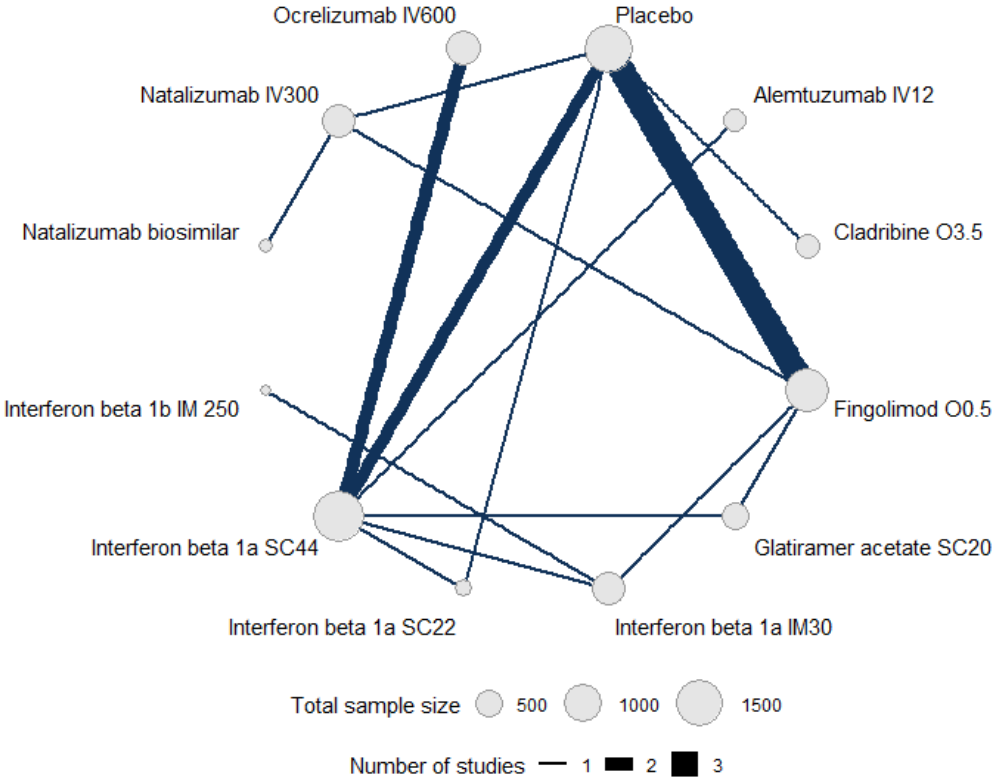
Figure 7 shows the hazard ratio (HR) and 95% credible intervals (CrI) for comparison of each intervention included in the network with placebo under the selected fixed effects model, stratified to show estimates from direct and indirect evidence and the overall NMA estimate. Comparison of estimates derived from direct and indirect evidence were similar. All interventions were associated with a greater reduction (i.e., HR<1 AND 95% CrI excluding 1.00) in the risk of developing Gd+ lesions compared to placebo. Results were very similar for both random and fixed effects models (Table 79 in Appendix 5). The ranking of interventions and the probability that each intervention would be ranked first is shown in Table 8, with Table 81 (Appendix 5) showing the probability that each intervention will rank in a specific position. Ocrelizumab had the highest mean ranking (1.4, 95 % CrI 1, 3) and the greatest probability of ranking first (68%) followed by natalizumab biosimilar (2.1, 95 % CrI 1, 4; 30%) and natalizumab (2.9, 95% CrI 2, 4; 1%). All other interventions had a 0% probability of ranking first. The different interferon and glatiramer acetate interventions were ranked similarly to each other and as less effective than the newer drugs. Table 80 (Appendix 4) shows the HR (95% CrI) for each intervention pair comparison evaluated in the NMA. This shows that the HR (95% CrI) for natalizumab compared to natalizumab biosimilar,

the key comparison for this appraisal, was 1.29 (0.69, 2.37), suggesting no difference between the HR for these two interventions.

New or enlarging T2 weighted lesions

The 17 studies (8,883 participants) that reported data on T2 weighted lesions created a connected network for 12 interventions of interest for this appraisal (Figure 1). The placebo group served as the reference group throughout.

Figure 12 Network plot for NMA for proportion of participants with new or enlarging T2 lesions



The DIC (26.4 vs 27.9) and residual deviance (15.4 vs 15.6 on 18 data points) were very similar for both fixed and random effects models and indicated good fit for both models with limited heterogeneity in treatment effects across studies (Table 82). This was confirmed by the heterogeneity standard deviation estimated by the random effects model (tau 95% of 0.07 (0.002, 0.25) in Table 82). We therefore present results for the fixed effect models for this outcome. Figure 37 (Appendix 5) shows how well each study fits the NMA model. The fixed effects model had a good fit to the data from all studies included in the network, except the IMPROVE study. This study reported data at very short follow-up (4 months) and compared interferon beta 1a SC44 to placebo.

Figure 8shows the hazard ratio (HR) and 95% credible intervals (CrI) for comparison of each intervention included in the network with placebo under the selected fixed effects model, stratified to show estimates from direct and indirect evidence and the overall NMA

estimate. Comparison of estimates derived from direct and indirect evidence were similar. All interventions except interferon beta 1a SC44 were associated with a greater reduction (i.e., HR<1 AND 95% CrI excluding 1.00) fewer patients with new or enhancing T2 lesions compared to placebo. Results were very similar for both random and fixed effects models (Table 82 in Appendix 5). The ranking of interventions and the probability that each intervention would be ranked first is shown in Table 8, with Table 87 (Appendix 5) showing the probability that each intervention will rank in a specific position. Ocrelizumab had the highest mean ranking (2.2, 95 % CrI 1, 5) and a similar probability of ranking first (30%) to natalizumab biosimilar (3.0, 95 % CrI 1, 7; 31%) and interferon beta 1b (3.1, 95% CrI 1, 8; 32%). Natalizumab had the next highest ranking (3.5, 95% CrI 1, 6) and a 4% probability of ranking first, followed by cladribine (4.2, 95% CrI 1, 7; 3%). All other interventions had a 0% probability of ranking first. The different interferon beta 1a and glatiramer acetate interventions were ranked similarly to each other and as less effective than the newer drugs. Table 83 (Appendix 4) shows the HR (95% CrI) for each intervention pair comparison evaluated in the NMA. This shows that the HR (95% CrI) for natalizumab compared to natalizumab biosimilar, the key comparison for this appraisal, was 1.07 (0.73, 1.57) suggesting no difference between the HR for these two interventions.

5.1.5 Adverse events

All but four of the included studies reported at least one of the adverse events outcomes of interest. Etemedifir 2006 and Calabrese 2012 did not report any data on adverse events; INCOMIN and PRISMS only reported data on the incidence of specific adverse events and so could not be included in our synthesis. Adverse events reported in the studies included a range of symptoms and reactions. These encompass injection site issues such as erythema, pain, pruritus, swelling, bruising, and immediate post-injection reactions, as well as systemic symptoms like influenza-like illness, chills, pyrexia, and fatigue. Common neurological and musculoskeletal complaints included headache, migraine, myalgia, arthralgia, dizziness, blurred vision, paraesthesia, and muscular weakness. Infections were frequently noted, including nasopharyngitis, urinary tract infections, upper respiratory tract infections, oral herpes, bronchitis, sinusitis, and meningitis. Other adverse events span gastrointestinal symptoms like nausea, diarrhoea, constipation, and abdominal pain, alongside more serious conditions such as hepatic toxicity, liver failure, and neoplasms. Psychiatric conditions, particularly depression and anxiety, were reported, as were dermatological issues like rash, alopecia, and hypoesthesia. Cardiovascular effects such as hypertension and bradycardia were also mentioned. Additionally, rare but serious conditions included autoimmune events and thyroid disorders.

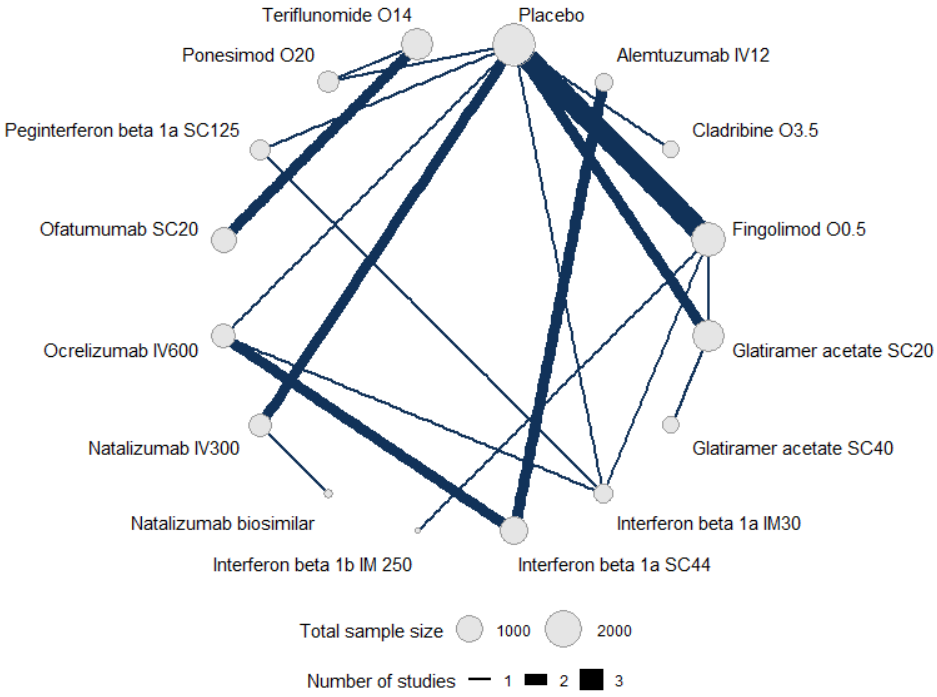
Mortality (from any cause) was only reported in 27 trials, and where reported this was very rare. The majority of studies reported no deaths, with a maximum of 2 deaths in any treatment group. Only four studies reported on progressive multifocal leukoencephalopathy (PML) – none of these reported any cases of PML. None of the included studies reported data on grade 3-4 AEs.

Twenty studies were judged at low risk of bias for adverse events, eleven were judged at some concerns and five were judged at high risk of bias.

Any AEs

Twenty four studies (14,513 participants) reported data on the incidence of any adverse events. These studies created a connected network for 16 interventions of interest for this appraisal (Figure 13) – the only intervention for which data on any AEs were not available was interferon beta 1a (SC22). The placebo group served as the reference group throughout. Follow-up duration ranged from 6 to 24 months with a median of 18 months – slightly shorter than for the effectiveness outcomes.

Figure 13 Network plot for NMA for any AEs



The DIC for the fixed effects model was lower than for the random effects model (32.6 vs 34.8), suggesting that this model gives a better trade off between fit and complexity for the dataset (Table 85). The residual deviance was also lower for the fixed effects model (17.8 vs 18.7 on 25 data points). However both indicated good fit for their respective models. The DIC and residual deviance together indicate limited heterogeneity in treatment effects across studies. This was confirmed by the heterogeneity standard deviation estimated by the random effects model (tau (95% CrI) of 0.03 (0.002, 0.11) in Table 85). We therefore present results for the fixed effects model for this outcome. Figure 38 (Appendix 5) shows how well each study fits the NMA model. The fixed effects model had a good fit to the data from all studies included in the network.

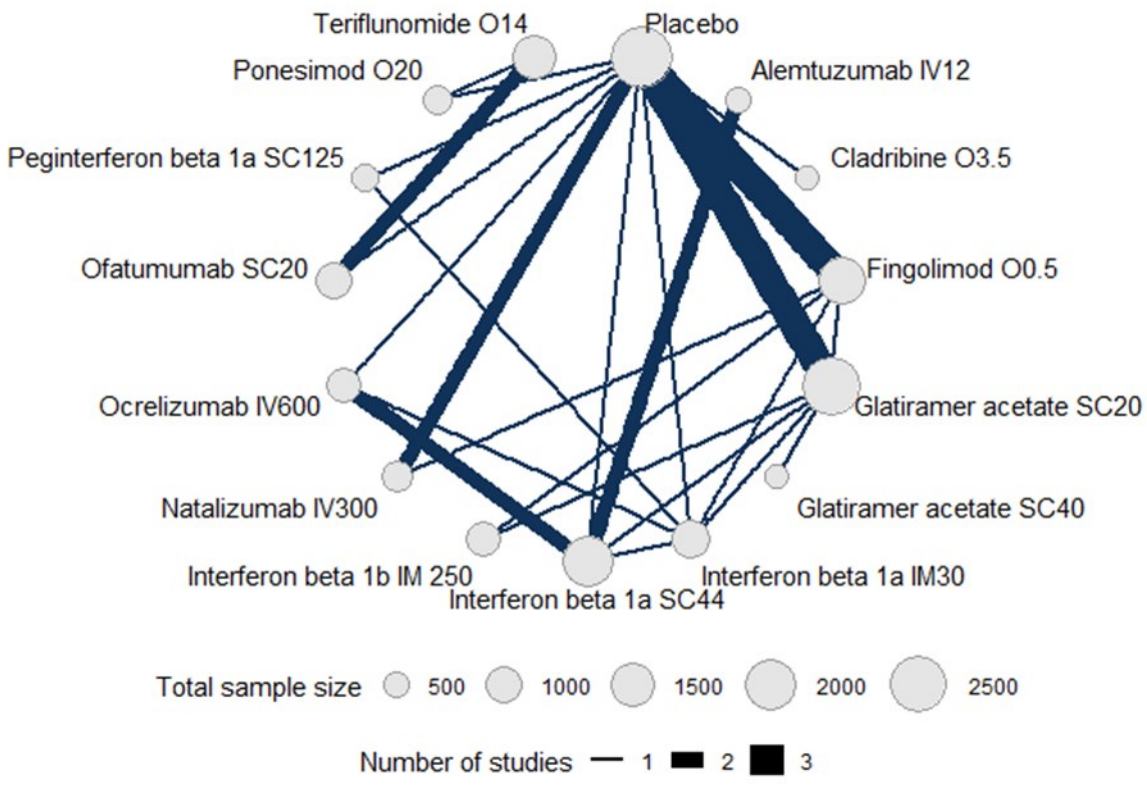
Figure 16 shows the hazard ratio (HR) and 95% credible intervals (CrI) for comparison of each intervention included in the network with placebo under the selected fixed effects model, stratified to show estimates from direct and indirect evidence and the overall NMA estimate. Comparison of estimates derived from direct and indirect evidence were similar. There was no evidence of a difference in the risk of developing any AE between any of the interventions and placebo (i.e., HR<1 AND 95% CrI excluding 1.00). Results were very similar

for both random and fixed effects models (Table 85 in Appendix 5). Table 87 (Appendix 5) showing the probability that each intervention will rank in a specific position with better rankings suggesting a lower risk of AEs. Table 86 (Appendix 4) shows the HR (95% CrI) for each intervention pair comparison evaluated in the NMA. This shows that the HR (95% CrI) for natalizumab compared to natalizumab biosimilar, the key comparison for this appraisal, was 1.06 (0.79, 1.45) suggesting no difference between the HR for these two interventions.

Serious AEs

Thirty one studies (18, 149 participants) reported data on the incidence of serious adverse events (SAEs). These studies created a connected network for 15 interventions of interest for this appraisal (Figure 13Figure 11) – data on any SAEs were not available for interferon beta 1a (SC22)or natalizumab biosimilar. The placebo group served as the reference group throughout. Duration of follow-up ranged from 6 to 36 months with a median of 18 months.

Figure 14 Network plot for NMA for serious AEs



The DIC for the fixed effects model was slightly lower than for the random effects model (38.8 vs 40.1), suggesting that this model gives a better trade off between fit and complexity for the dataset (Table 88). Both models have residual deviances lower than the number of data points (24.7 vs 24.2 on 32 data points) with the fixed effects model suggesting a slightly better fit. The DIC and residual deviance together indicate limited heterogeneity in treatment effects across studies. This was confirmed by the heterogeneity standard deviation estimated by the random effects model (tau (95% CrI) of 0.11 (0.001, 0.33) in Table 88). We therefore present results for the fixed effect models for this outcome. Figure

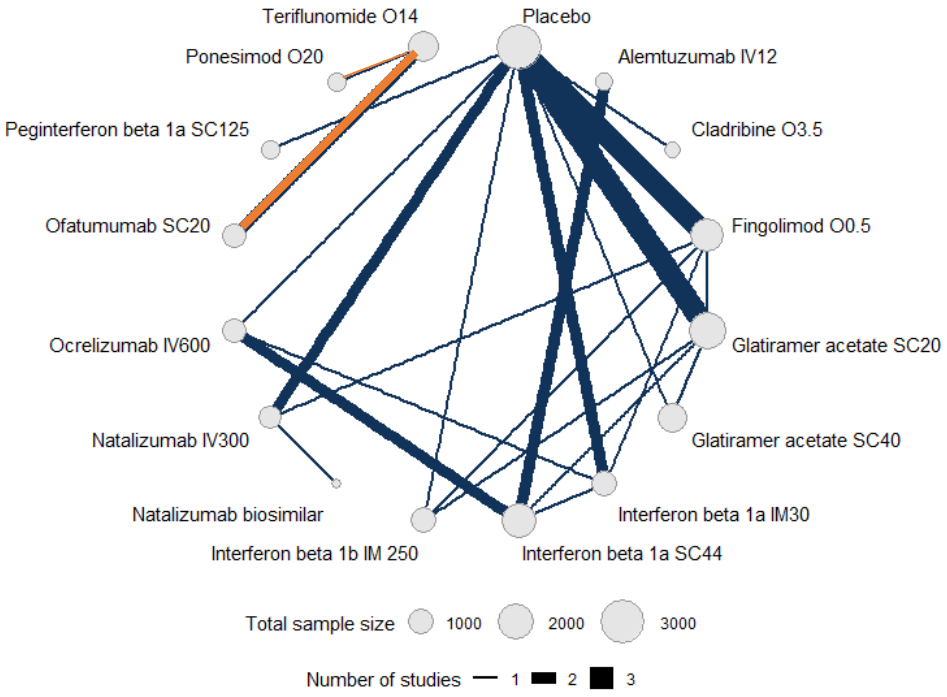
39 shows how well each study fits the NMA model. Although FREEDOMS shows a higher residual deviance than the rest of studies, it's 95% CrI fall within the acceptable range, so we consider the fixed effects model had a good fit to the data from all studies included in the network.

Figure 17 shows the hazard ratio (HR) and 95% credible intervals (CrI) for comparison of each intervention included in the network with placebo under the selected fixed effects model, stratified to show estimates from direct and indirect evidence and the overall NMA estimate. Comparison of estimates derived from direct and indirect evidence were similar. There was no evidence of a difference in the risk of developing serious AE between any of the interventions and placebo (i.e., HR<1 AND 95% CrI excluding 1.00). Results were very similar for both random and fixed effects models (Table 88 Comparison of results from fixed and random effects NMA for SAEs (RRMS population)Table 85 in Appendix 5). Table 90 (Appendix 5) shows the probability that each intervention will rank in a specific position. Table 89 shows the HR (95% CrI) for each intervention pair comparison evaluated in the NMA. There was no data on frequency of serious AE for natalizumab biosimilar, so a comparison to Natalizumab was not possible.

AEs leading to treatment discontinuation

Twenty nine studies (17,892 participants) reported data on the incidence of AEs leading to treatment discontinuation. These did not create a completely connected network – teriflunomide, ponesimod and ofatumumab did not connect to the network (Figure 15). We were therefore unable to include these interventions in the NMA. Data on any AEs leading to treatment discontinuation were not available for interferon beta 1a (SC22) and this was also not included in the network. The placebo group served as the reference group throughout.

Figure 15 Network plot for NMA for AEs leading to treatment discontinuation including disconnected treatments (shown with orange lines)



The DIC for the fixed effects model was slightly lower than for the random effects model (41.2 vs. 41.7), suggesting that this model gives a slightly better trade-off between fit and complexity for the dataset (Table 91). Both models have residual deviances close to the number of data points (29.2 vs 26 on 28 data points) with the fixed effects model suggesting a slightly better fit. The DIC and residual deviance together indicate limited heterogeneity in treatment effects across studies. This was confirmed by the heterogeneity standard deviation estimated by the random effects model (tau (95% CrI) of 0.27 (0.01, 0.69) in Table 91). We therefore present results for the fixed effect models for this outcome. Figure 40 Model fit for discontinuation due to AEs assessed by individual study residual deviance (fixed effects analysis; RRMS population) shows how well each study fits the NMA model. Although FREEDOMS and TRANSFORMS show a higher residual deviance than the rest of studies, its 95% CrI fall within the acceptable range. GATE shows a high residual deviance, but this is a very small study, so we consider the fixed effects model had a good fit to the data from studies included in the network in general.

Figure 18 shows the hazard ratio (HR) and 95% credible intervals (CrI) for comparison of each intervention included in the network with placebo under the selected fixed effects model, stratified to show estimates from direct and indirect evidence and the overall NMA estimate. Comparison of estimates derived from direct and indirect evidence were similar. There was evidence of an increased risk of presenting with an adverse event leading to discontinuation for fingolimod HR (95% CRI), glatiramer acetate, interferon beta 1a SC44, interferon beta 1b, and peginterferon beta 1a compared with placebo. There was no evidence of a difference in the risk of AEs leading to treatment discontinuation between any of the other interventions and placebo. Results were very similar for both random and fixed effects models (Table 91 in Appendix 5). Table 93 (Appendix 5) shows the probability that each intervention will rank in a specific position. Table 92 shows the HR (95% CrI) for each intervention pair comparison evaluated in the NMA. This shows that the HR (95% CrI) for natalizumab compared to natalizumab biosimilar, the key comparison for this appraisal, was 0.48 (0.13, 1.76) suggesting no difference between the HR for these two interventions.

Treatment related AEs

Only eight studies (3,361 participants) reported data on treatment related adverse events. These did not create a connected network and so an NMA was not possible. Instead, we provide a summary of the results from these studies in Table 9. Interventions evaluated included Peginterferon beta 1a, natalizumab, natalizumab biosimilar, ofatumumab, ocrelizumab, glatiramer acetate, interferon beta 1a, and peginterferon beta 1a. There was no difference between interventions in the proportion of treatment related AEs for any of the studies.

Table 9 Summary of studies that reported data on treatment related AEs, including RR and 95% CIs for the difference in risk between intervention and comparator groups

Study Name	Intervention	Comparator	Follow-up	RR (95% CI)
ADVANCE[80]	Peginterferon beta 1a SC125	Placebo	12	1.69 (0.54, 0.65)
ANTELOPE[76]	Natalizumab IV300	Natalizumab biosimilar	6	1.11 (0.56, 1.46)
APOLITOS[69]	Ofatumumab SC20	Placebo	6	0.86 (0.87, 1.54)
CONFIDENCE[88]	Glatiramer acetate SC40	Glatiramer acetate SC20	6	1.0 (0.83, 1.21)
Kappos 2011[100]	Interferon beta 1a IM30	Placebo	6	0.76 (0.83, 2.09)
	Ocrelizumab IV600	Placebo	6	0.67 (0.92, 2.44)
PEGINTEGRITY[65]	Peginterferon beta 1a SC125	Interferon beta 1a IM30	24	0.94 (0.9, 1.25)
REGARD[103]	Glatiramer acetate SC20	Interferon beta 1a SC44	24	0.99 (0.89, 1.11)
REVEAL[78]	Natalizumab IV300	Fingolimod O0.5	6	0.72 (0.95, 2.04)

5.1.6 Quality of life

Only eight studies provided data on quality of life assessed using the EQ-5D or SF-36 tools. Results from these studies are summarised in Table 60 (Appendix 4). Six studies provided data on the SF-36 (ADVANCE, CARE-MS I, CONFIRM, AFFIRM, OPERA I, OPERA II) and five studies provided data on EQ-5D (CLARITY, FREEDOMS II, ADVANCE, CARE-MS I, CONFIRM). Four studies were judged at high risk of bias, three were at low risk of bias, and one was at low concerns for the EQ-5D visual analogue scale and some concerns for the EQ-5D utility score and SF-36 measures.

There was no evidence of a difference between groups for any of the studies that reported data on the EQ-5D mean utility or VAS scores. Interventions evaluated in these studies were cladribine, fingolimod, peginterferon beta and glatiramer acetate vs placebo and alemtuzumab vs interferon beta 1a. Three studies (ADVANCE, AFFIRM and CARE-MS I) reported no differences between groups for either the physical component summary (PCS) or mental component summary (MCS) component of the SF-36. These studies compared peginterferon beta 1a and natalizumab with placebo and alemtuzumab with interferon beta 1a. The CONFIRM study reported a greater improvement in PCS with glatiramer acetate than with placebo ($p<0.05$) but found no difference for MSC. OPERA I reported no difference in change from baseline in PCS between ocrelizumab and interferon beta 1a ($p=0.22$), while OPERA II found a greater improvement in PCS with ocrelizumab compared to placebo ($p=0.04$).

A further four studies provided data on QoL but did not use the standard EQ-5D or SF-36 specified as in scope for this appraisal. The used the MSQoL-54[108] (GOLDEN, PEGINTEGRITY), MSIS-29 (ASSESS)[109] and a 0-100 VAS to measure global wellbeing VAS (Saida 2017).

5.1.7 Summary

Table 10 provides an overview of the results for each outcome in the general RRMS population. For each outcome, it provides a summary of the number of studies that contributed to the synthesis, the number of interventions included in the synthesis and any interventions for which data were not available for this outcome, the most and least effective interventions, and any information available on the comparison of natalizumab biosimilar and natalizumab, or where data were not available on natalizumab biosimilar we summarise evidence on natalizumab compared to placebo.

Figure 16 Forest plot of hazard ratio (HR) and 95% credible intervals for time to developing at least one adverse event (fixed effects NMA; RRMS population).

Blue lines indicate result from the NMA, green lines indicate results from direct evidence and purple lines from indirect evidence. P-values relate to comparisons between direct and indirect evidence. Note that the indirect evidence lines are only included if there is also direct evidence

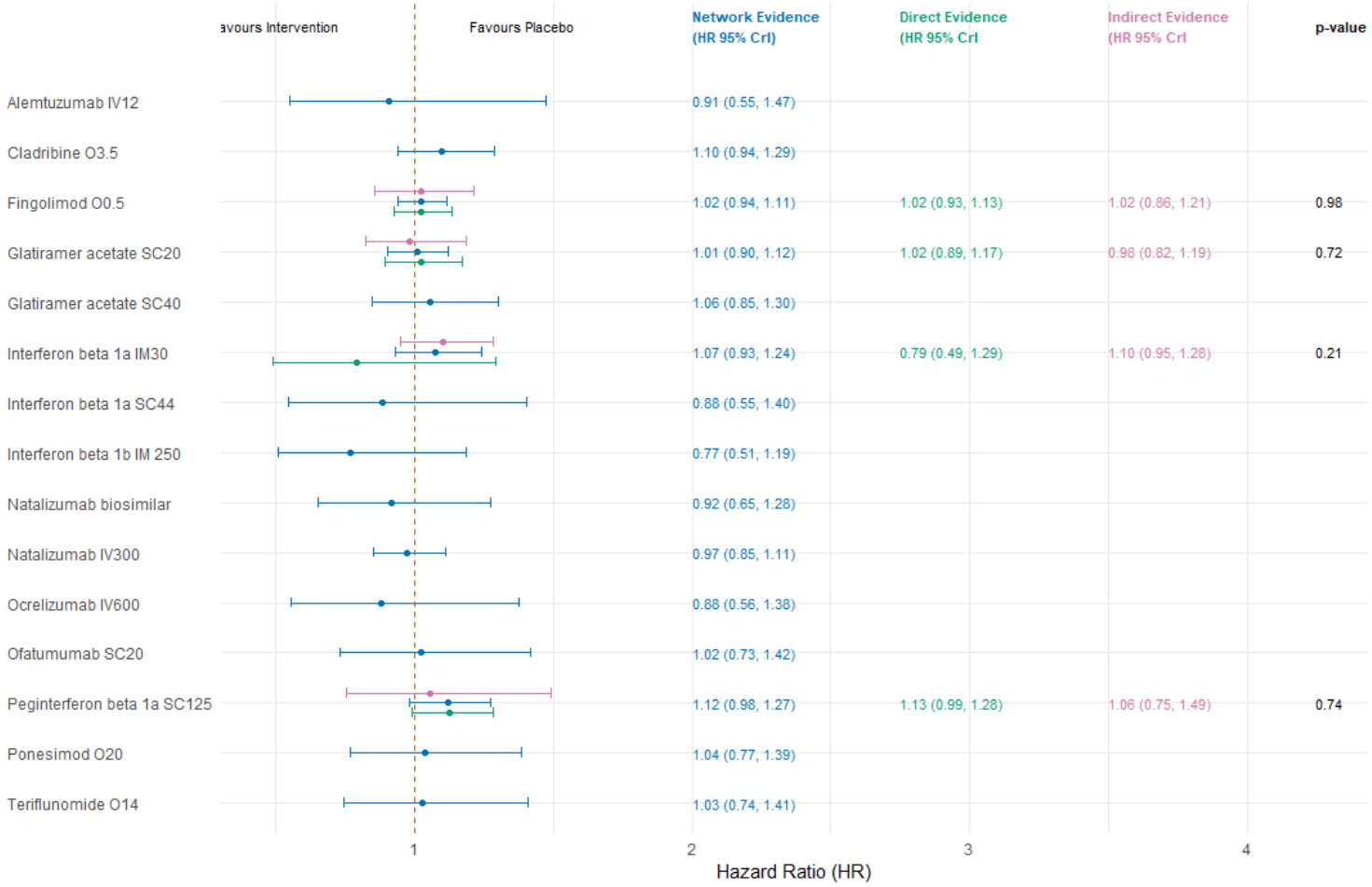


Figure 17 Forest plot of hazard ratio (HR) and 95% credible intervals for time to developing at least one serious adverse event (fixed effects NMA; RRMS population).

Blue lines indicate result from the NMA, green lines indicate results from direct evidence and purple lines from indirect evidence. P-values relate to comparisons between direct and indirect evidence. Note that the indirect evidence lines are only included if there is also direct evidence

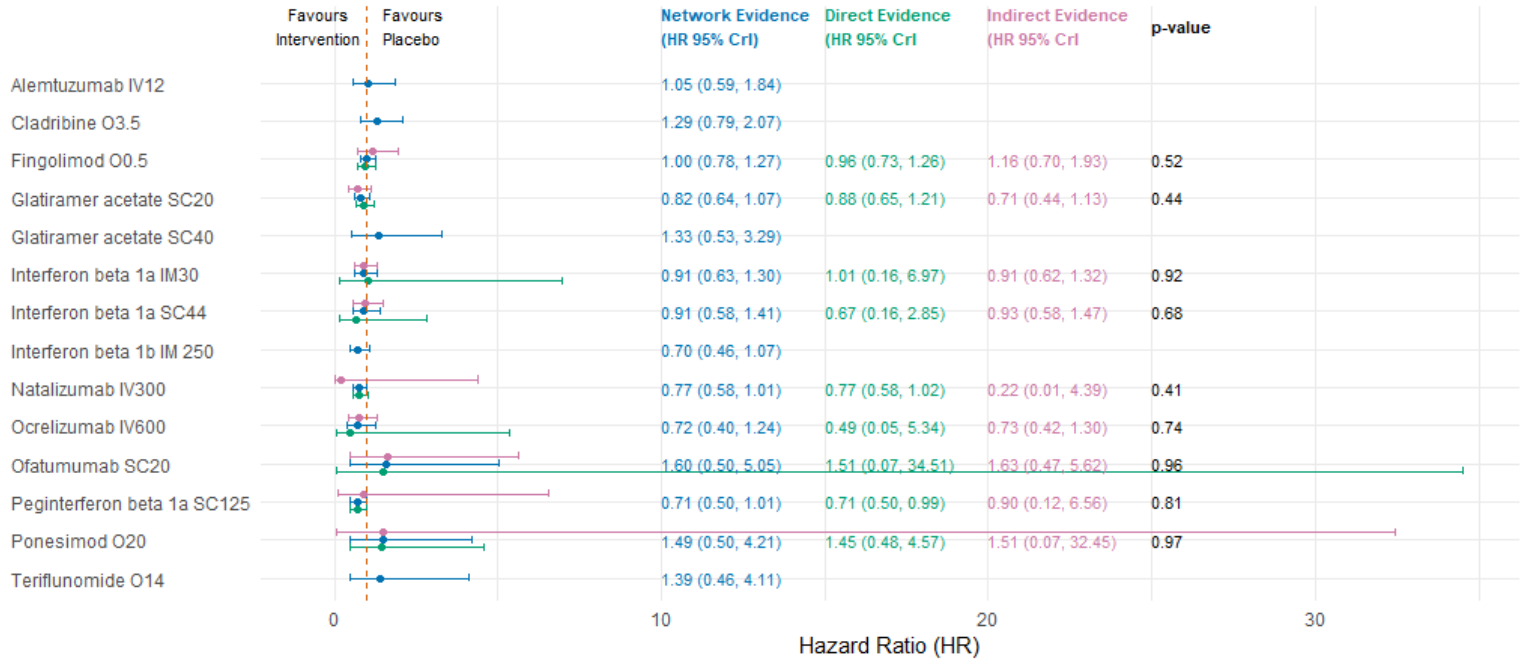


Figure 18 Forest plot of hazard ratio (HR) and 95% credible intervals for time to treatment discontinuation (fixed effects NMA; RRMS population).

Blue lines indicate result from the NMA, green lines indicate results from direct evidence and purple lines from indirect evidence. P-values relate to comparisons between direct and indirect evidence. Note that the indirect evidence lines are only included if there is also direct evidence

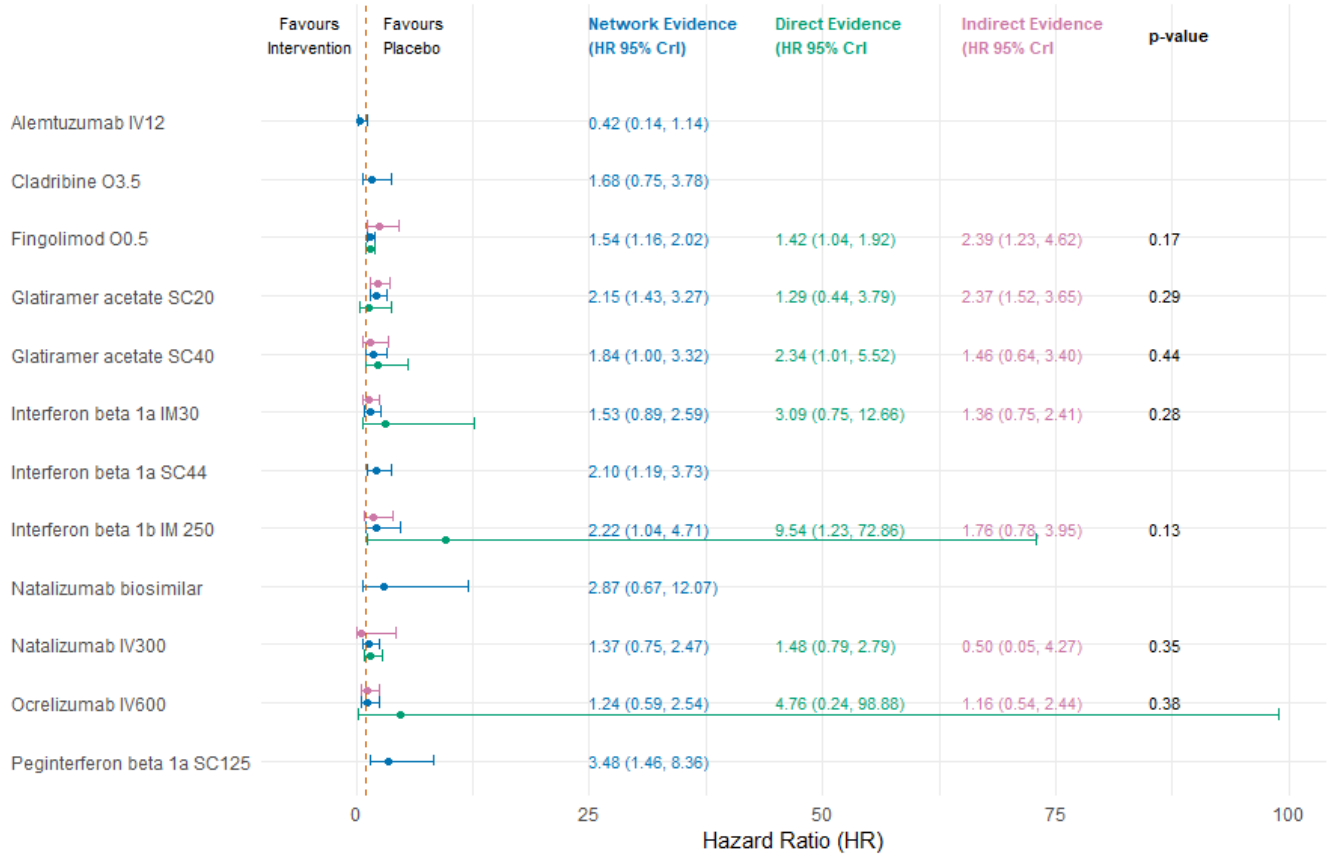


Table 10 Summary of results for each outcome evaluated in the RRMS studies

Outcome	Number of studies (participants)	Number of interventions in network	Interventions excluded from network/synthesis	Most effective interventions	Least effective interventions	Data on Natalizumab and Natalizumab biosimilar
ARR	39 (20, 718)	17	AHSCT	Alemtuzumab, natalizumab and ocrelizumab	Interferon beta, glatiramer acetate, ponesimod, teriflunomide	Natalizumab vs natalizumab biosimilar: RR 0.65 (95% CI 0.34, 1.26) from NMA
CDP3	15 (10, 824)	12	AHSCT, teriflunomide, ponesimod, ofatumumab, natalizumab biosimilar, glatiramer acetate SC40	Alemtuzumab, cladribine, fingolimod, natalizumab, ocrelizumab, interferon beta 1a (SC22 & 44) and peginterferon beta 1a	Other interferon beta and glatiramer acetate	Natalizumab vs placebo HR 0.58 (0.43, 0.76) from NMA
CDP6	14 (9,006)	11	AHSCT, teriflunomide, ponesimod, ofatumumab, natalizumab biosimilar, glatiramer acetate SC40, interferon beta 1a SC22	Alemtuzumab, fingolimod, natalizumab ocrelizumab, interferon beta 1b and peginterferon beta 1a	Other interferon beta, glatiramer acetate, cladribine	Natalizumab vs placebo: HR 0.46 (0.33, 0.63) from NMA
MRI Gd+	19 (9471)	11	AHSCT, ofatumumab, interferon beta 1a (SC22), glatiramer acetate (SC40), ponesimod, teriflunomide, peginterferon beta 1a	Alemtuzumab, cladribine, fingolimod, natalizumab, natalizumab biosimilar, ocrelizumab, interferon beta 1b	Interferon beta 1a and glatiramer acetate	Natalizumab vs natalizumab biosimilar: HR 1.29 (0.69, 2.37) from NMA
MRI T2	17 (8,883)	12	AHSCT, ofatumumab, glatiramer acetate (SC40), ponesimod, teriflunomide, peginterferon beta 1a	Alemtuzumab, cladribine, fingolimod, natalizumab, natalizumab biosimilar, ocrelizumab, interferon beta 1b	Interferon beta 1a and glatiramer acetate	Natalizumab vs natalizumab biosimilar: HR 1.07 (0.73, 1.57) from NMA
AEs: Any	24 (14513)	16	AHSCT, interferon beta 1a (SC22),	No evidence of a difference between interventions		Natalizumab vs natalizumab biosimilar: HR 1.06 (0.79, 1.45) from NMA

Outcome	Number of studies (participants)	Number of interventions in network	Interventions excluded from network/synthesis	Most effective interventions	Least effective interventions	Data on Natalizumab and Natalizumab biosimilar
AEs: SAE	30 (18, 149)	14	AHSCT , iterferon beta 1a (SC22), cladribine, natalizumab biosimilar	No evidence of a difference between interventions		Natalizumab vs placebo: HR 0.77 (0.58, 1.00); no data on natalizumab biosimilar
AEs: Treatment discon-tinuation	29 (17, 892)	13	AHSCT, ofatumumab, interferon beta 1a (SC22), ponesimod, teriflunomide	No evidence of a difference for all other interventions	Fingolimod, glatiramer acetate, interferon beta 1a (SC44), interferon beta 1b, & peginterferon beta 1a	Natalizumab vs natalizumab biosimilar: HR 0.48 (0.13, 1.76) from NMA
Treatment related AEs	8 (3,361)	7	All except: Peginterferon beta 1a, natalizumab, natalizumab biosimilar, ofatumumab, glatiramer acetate, interferon beta 1a, ocrelizumab	No evidence of a difference between interventions		Natalizumab vs natalizumab biosimilar: RR 1.11 (0.56, 1.46) from ANTELOPE[76]
Quality of Life	8	4	All except: cladribine, fingolimod, peginterferon beta and glatiramer acetate	Little evidence of any effect on QoL		No data

5.2 Highly active MS (HARRMS) population

Eight studies (2,097 participants) reported data on patients with HARRMS. Two of these studies (CARE-MS II[71] and MIST[72]) were conducted exclusively in patients with HARRMS the others were conducted in the general RRMS population but reported results separately for the highly active population. For OPERA I & II[67] and for FREEDOMS and FREEDOMS II[73], results were only available for the two studies combined – we therefore consider these as single studies in this section. None of the studies evaluated natalizumab or natalizumab biosimilar, the technologies of interest for this appraisal. However, one of the studies that compared natalizumab with placebo was conducted in a population where participant were required to have had at least one relapse in the previous year and a very high proportion of participants (88%) had previously been treated with a DMT (IFN beta 1a, IFN beta 1b, azathioprine, or fingolimod) – this was close to the definition that we set in section 4.3.6 of at least 90% having highly active disease. This study was conducted exclusively in Japanese patients. We included this study in the analysis for the HARRMS population as the best available evidence. However, this study only reported data on ARR and AEs.

Table 5 provides an overview of the interventions evaluated by the included studies. Interventions evaluated in the HARRMS included: fingolimod, ocrelizumab, alemtuzumab, and cladribine with Saida 2017 evaluating natalizumab. Two studies included a placebo control group, four studies included beta-interferon as the comparator and one compared AHSCT to a DMT as chosen by the investigators.

Table 49 (Appendix 3) provides a summary of the baseline characteristics of participants included in the HARRMS studies. OPERA I/II[67] did not report baseline characteristics separately for the HARRMS population. For the other studies, mean age ranged from 35 to 39 years (median 37 years – similar to the overall RRMS population), the proportion of female participants ranged from 62 to 76% (median 69%, also similar to the overall RRMS population), baseline EDSS score from 1.0 to 3.5 (median 2.7 – slightly higher than overall RRMS), baseline annual relapse rate was only reported for CARE-MS II and FREEDOMS II and ranged from 1.5 to 1.7 (lower than RRMS population), and mean disease duration at baseline ranged from 4.5 to 7 years (median 6.2 years), ethnicity was not reported in these studies. All participants had received previous treatment with DMTs – the actual treatments varied across studies but generally included interferon beta 1a, interferon beta 1b, and glatiramer acetate. Publication years ranged from 2010 to 2019.

Definitions of highly active disease varied across studies – all required previous treatment with DMT, some definitions specified that this should have been either interferon beta or glatiramer acetate others did not specify which treatments. Studies also included requirements for relapses in the previous year, despite treatment, but the specific requirements varied across studies from at least one relapse in the previous year with MRI evidence of progression, at least the same number of relapses in the previous year as in the previous 2 years or the preceding year.

5.2.1 Risk of bias

Table 11 provides a summary of the risk of bias assessment for studies in the HARRMS population, stratified according to outcome. Results tables in Appendix 4 also include the overall risk of bias for each study for each outcome evaluated. All studies had the same

overall risk of bias judgement for all outcomes; three (CARE-MS II, MIST and FREEDOMS I/II) were judged at high risk of bias – in CARE-MS II and MIST participants were aware of treatment allocation, and in FREEDOMS II there was a large proportion of missing data which was considered potentially related to the outcome. The CLARITY study was judged at some concerns as there was missing data, but all randomised participants were included in the analysis. The other two studies in the HARRMS population (FREEDOMS and TRANSFORMS) and Saida 2017 were judged at low risk of bias.

5.2.2 Annualised Relapse Rate (ARR)

All studies except MIST reported data on ARR. The studies did not create a connected network, but by assuming a class effect for the two different interferon beta 1a comparators (IM30 and SC44) and combining these into a single node we were able to create a connected network.

We therefore included six studies (2,162 participants) evaluating seven interventions in the NMA for ARR in the highly active population. The network geometry for this analysis is shown in Figure 19. The placebo group served as the reference group throughout. The DIC for the fixed effects model was similar to that for the random effects model (16.2 vs 16.1) (Table 94). The residual deviance was very similar for both fixed and random effects (8.1 vs 8.0 on 8 data points) and indicated good fit for both models. The heterogeneity standard deviation estimated by the random effects model (tau (95% CrI) of 1.40 (0.05, 3.95) inTable 94) was high when compared to the average treatment effect on the log rate ratio scale (-0.58 in Table 62) but its 95% CrI were wide suggesting limited evidence to estimate it, thus supporting the use of fixed effects. We therefore present results for the fixed effects model for this outcome. Figure 41 (Appendix 5) shows very good fit for each study to the NMA model.

Figure 19 Network plot for NMA for ARR (highly active population)

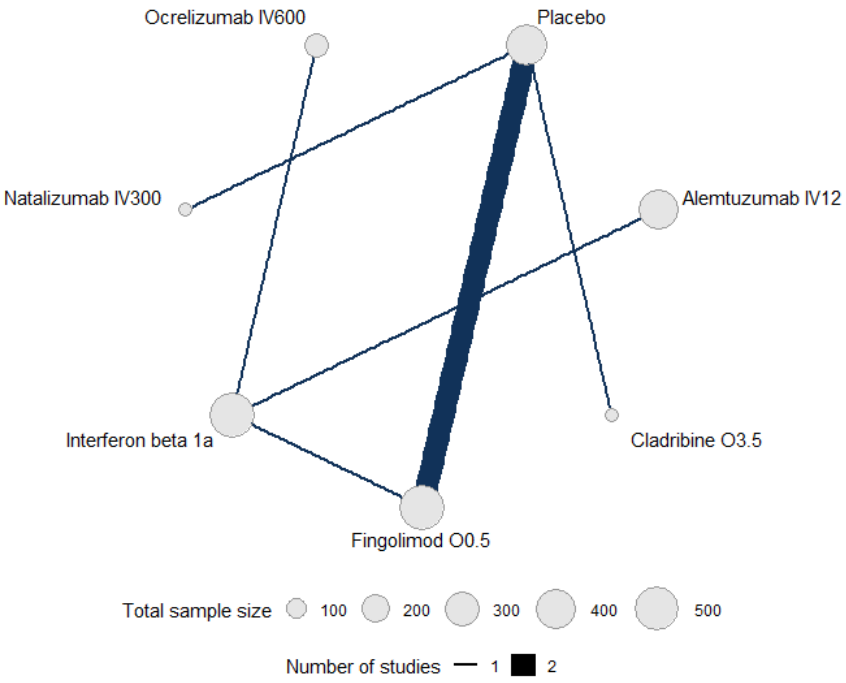
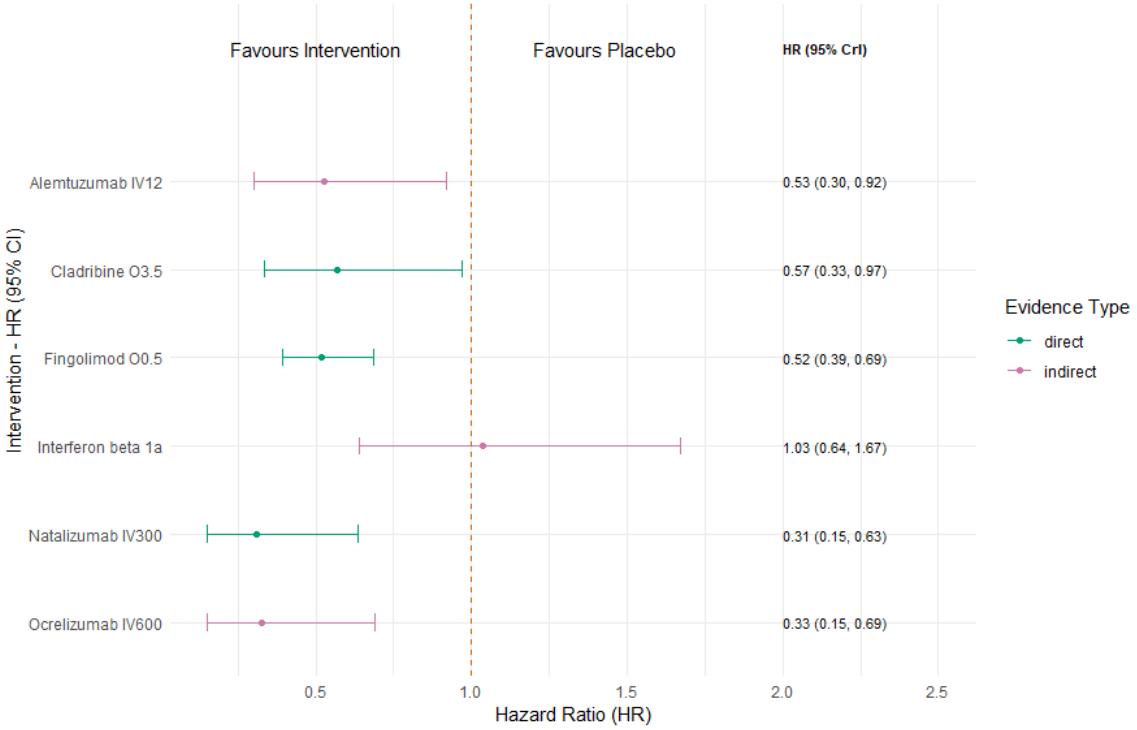


Figure 20 shows the rate ratio (RR) and 95% credible intervals (CrI) for comparison of each intervention included in the network with placebo. All interventions with the exception of interferon beta 1a were associated with a greater reduction (i.e., RR<1 AND 95% CrI excluding 1.00) in the risk of relapses compared to placebo. Results were similar for both random and fixed effects models, although credible intervals were very wide from random effects models (Table 94 in Appendix 5). The ranking of interventions and the probability that each intervention would be ranked first is shown in Table 8, with Table 96 (Appendix 5) showing the probability that each intervention will rank in a specific position. Ocrelizumab and natalizumab had the highest mean rankings (both 1.8 (95 CrI 1, 5)) with Natalizumab having a higher probability of ranking first (53% vs 44%). All other interventions in the network had ≤2% probability of ranking first. Table 95(Appendix 4) shows the RR (95% CrI) for each intervention pair comparison evaluated in the NMA.

Figure 20 Forest plot of rate ratios (RR) and 95% credible intervals from fixed effects NMA for ARR (fixed effects NMA; HA population).
Green lines indicate results from direct evidence and purple lines from indirect evidence.

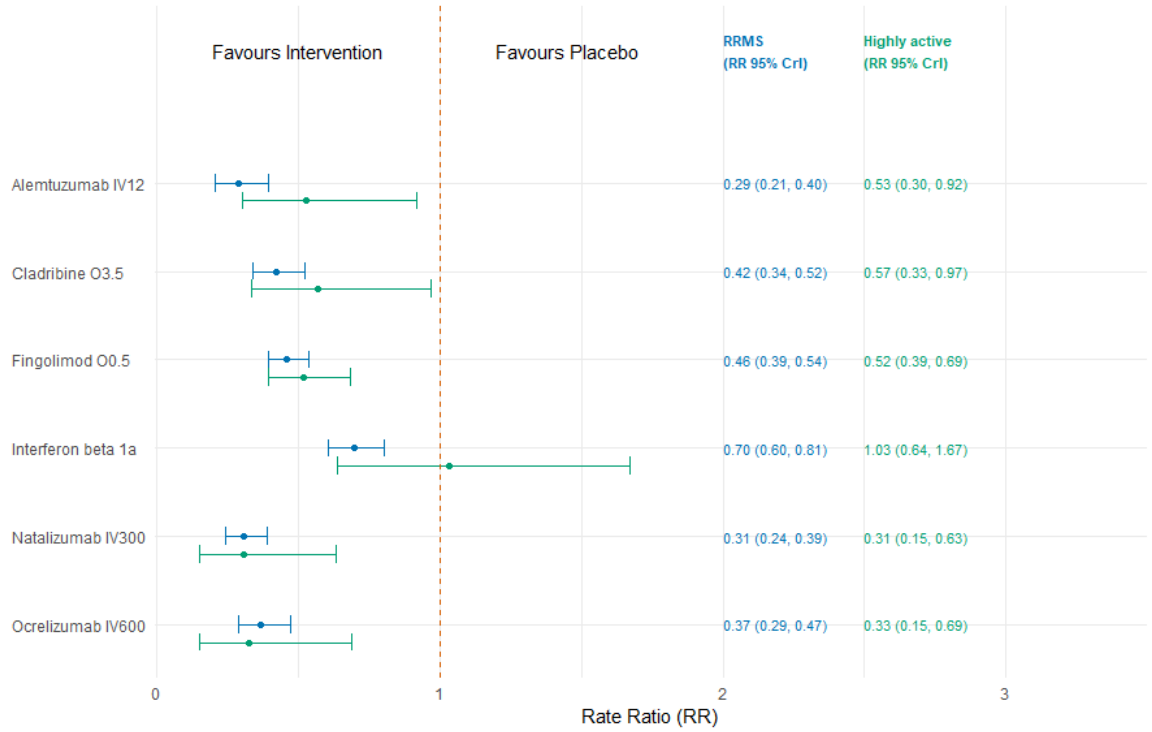


Comparison of ARR results between highly active and RRMS population

As we only had data on a limited number of interventions in the highly active population, we conducted an ad hoc analysis to determine whether there was any evidence of a difference in the relative effectiveness of interventions in the highly active and RRMS population. To allow direct comparisons between populations, we conducted a sensitivity analysis in the RRMS population where we restricted the network to the seven interventions in the network for ARR in the highly active population. As we had combined the interferon beta 1a interventions into a single node for the highly active population, we did the same for the RRMS population. Figure 21 shows that estimates of RR for ARR derived from the two different MS populations were very similar, although 95% credible intervals were wider in the highly active population. This would be expected as fewer studies contributed to these estimates.

Figure 21 Forest plot of rate ratios (RR) and 95% credible intervals from NMA for ARR in the highly active and RRMS populations (fixed effects NMA)

Blue lines indicate results in the general RRMS population and green lines in the highly active population



5.2.3 Disease progression

All studies except TRANSFORMS and Saida 2017 reported data on disease progression. Two studies reported data for CDP3 (CLARITY, FREEDOMS and OPERA I/II) and five reported data for CDP6 (CARE-MS II, CLARITY, FREEDOMS I/II, OPERA I/II and MIST). We could not create a connected network for either disease progression outcome and so a NMA was not performed. Results from these studies, including HRs and 95% CIs, are reported in Table 12. All interventions (alemtuzumab, cladribine, fingolimod, ocrelizumab and AHSCT) were associated with a reduced risk of disease progression confirmed at both 3 and 6 months compared to comparator interventions (interferon beta 1a, placebo or iDMT). To allow comparison of the effect in the highly active population and the general RRMS population we also included data from these studies in the RRMS population in Table 12. There were no clear differences in effect between the highly active or general RRMS population for disease progression, although HR estimates tended to be slightly lower (i.e. suggesting greater effect) in the highly active population, 95% CIs were wide and overlapped with those from estimates from the general RRMS population.

5.2.4 MRI outcomes

CARE-MS II was the only study to report data on MRI outcomes in the HARRMS population. This study reported that alemtuzumab was associated with a lower risk of both Gd+ lesions (RR 0.40, 95% CI 0.27, 0.60) and new or enlarging T2 lesions (RR 0.68, 95% CI 0.59, 0.79) than beta interferon 1a. The related CARE-MS I study, which was conducted in the general

RRMS population, reported similar results - alemtuzumab was associated with a lower risk of both Gd+ lesions (RR 0.37, 95% CI 0.23, 0.60) and new or enlarging T2 lesions (RR 0.84, 95% CI 0.71, 0.99) than beta interferon 1a.

5.2.5 Adverse events

CARE-MS II was the only study to report data on adverse events specifically in the HARRMS population. Data on adverse event were also available for Saida 2017 – these are included in the analysis for the general RRMS population and suggest fewer AEs in the Natalizumab arm compared to placebo, although with no strong evidence of a difference between groups. CARE-MS II reported that alemtuzumab was associated with a very small increased risk of any adverse event (RR 1.04, 95% CI 1.00, 1.08) but a lower risk of treatment discontinuation (RR 0.43, 95% CI 0.21, 0.88) than beta interferon 1a. There was no difference in the risk of serious AEs (RR 0.83, 95% CI 0.67, 1.04). Comparison with the related CARE-MS I study suggested similar results for serious AEs (RR 0.79, 95% CI 0.52, 1.18). However, there was a very small decreased risk of any adverse event (RR 0.94, 95% CI 0.90, 0.99) and a large increased risk of treatment discontinuation (RR 4.42, 95% CI 1.56, 12.55) for alemtuzumab compared to beta interferon 1a. Both CARE-MS I and II were judged at high risk of bias.

5.2.6 Quality of life (QoL)

CARE-MS II and MIST were the only studies to report data on adverse events in the highly active MS population. Both studies were judged at high risk of bias. MIST reported that QoL was better in those treated with AHCT compared to those in the comparator DMT group ($p<0.001$). CARE-MS II found no difference between groups in the SF-36 MCS score, but a significantly greater improvement with alemtuzumab on the PCS score compared to interferon beta 1a. The related CARE-MS I study, conducted in the general RRMS population, found no difference in QoL between intervention groups.

Table 11 Risk of bias for studies in the HARRMS population

Study	Outcome	Domain					Overall	Rationale
		1	2	3	4	5		
CARE-MS II[71]	ARR; MRI; AE; QoL	Low	High	Some concerns	Low	Low	**High**	Patients and carers were aware of the treatment assignments; missing outcome data but sensitivity analyses performed
CLARITY[86]	ARR; CDP	Low	Low	Some concerns	Low	Low	**Some concerns**	Some missing data potentially related to outcome but all randomised participants included in analysis
FREEDOMS 1/II[110]	ARR; CDP	Low	Low	High	Low	Low	**High**	Large proportion of missing data potentially related to outcome
MIST[72]	CDP	Some concerns	High	Low	Low	Low	**High**	Patients and carers were aware of the treatment assignments
	QoL					Some concerns		QoL not specified as outcome in trial registry entry - only outcome specified was disease progression
OPERA I/II[67]	ARR; CDP	Low	Low	Low	Low	Low	**Low**	No concerns
Saida 2017[79]	ARR; AE	Low	Low	Low	Low	Low	**Low**	No concerns
TRANSFORMS[75]	ARR; CDP; AE	Low	Low	Low	Low	Low	**Low**	No concerns

Domain 1: Risk of bias arising from the randomization process; Domain 2: Risk of bias due to deviations from the intended interventions; Domain 3: Risk of bias due to missing outcome data; Domain 4: Risk of bias in measurement of the outcome; Domain 5: Risk of bias in selection of the reported result
ARR: annualised relapse rate; CDP: confirmed disease progression; AE: adverse event; QoL: Quality of Life

Table 12 Estimates of HR and 95% CIs for disease progression confirmed at 3 (CDP3) and 6 (CDP6) months in the highly active and general RRMS populations from studies that reported data in people with HARRMS

Study Name	Intervention	Comparator	Follow-up (mths)	HARRMSpopulation		General RRMS Population	
				CDP3: HR (95% CI)	CDP6: HR (95% CI)	CDP3: HR (95% CI)	CDP6: HR (95% CI)
CARE-MS II[71] (HA) & CARE-MS I (RRMS)	Alemtuzumab	Interferon beta 1a (SC44)	24	NR	0.58 (0.38, 0.87)	NR	0.70 (0.40, 1.23)
CLARITY[86]	Cladribine	Placebo	24	0.25 (0.07, 0.89)	0.20 (0.04, 0.91)	0.67 (0.48, 0.93)	NR
FREEDOMS[74]	Fingolimod	Placebo	24	0.59 (0.29, 1.20)	0.50 (0.34, 0.90)	0.70 (0.52, 0.96)	1.59 (1.11, 2.27)
FREEDOMS II[73]	Fingolimod	Placebo	24	NR		0.83 (0.61, 1.12)	0.72 (0.48, 1.07)
OPERA II[67]	Ocrelizumab	Interferon beta 1a (SC44)	24	0.47 (0.23, 0.95)	0.50 (0.23, 1.09)	0.57 (0.37, 0.9)	0.57 (0.34, 0.95)
OPERA II[67]						0.63 (0.42, 0.92)	0.63 (0.40, 0.98)
MIST[72]	AHSCT	iDMT	34	NR	0.07 (0.02, 0.24)	NA	

6 Assessment of cost effectiveness

Sections of this Chapter have been reproduced from the study's Protocol document, available at the NICE website.[1]

6.1 Systematic review of existing cost-effectiveness evidence

We conducted a review to summarise evaluations of the cost effectiveness of interventions for highly active relapsing-remitting multiple sclerosis after at least one disease modifying therapy and to identify studies/evaluations reporting UK costs data to inform the model. The review followed the principles outlined in the Centre for Reviews and Dissemination (CRD) guidance for undertaking reviews in health care and the NICE Health Technology Evaluations Manual.[46, 47] The review is reported according to the PRISMA 2020 guidance [48]

6.1.1 Study identification

On the 15th May 2024, we searched:

- MEDLINE (MEDALL) 1946 to May 14, 2024;
- Embase 1974 to 2024 May 14;
- Econtlit 1981-current; and
- NHS Economic Evaluations Database (NHS EED) via https://www.crd.york.ac.uk/CRDWeb/HomePage.asp.

Economic evaluations identified by the clinical effectiveness searches were flagged by the reviewers for potential inclusion in the review of economic models.

6.1.2 Selection criteria

Studies were selected by two researchers if they reported an:

- economic evaluation in HARRMS; OR
- economic evaluation or costs study in RRMS if done in the UK.

We excluded evaluations where the focus was on the perspectives of payers in countries other than the UK to align our review to the needs of NICE decision-makers.

6.1.3 Results

A flowchart detailing the study identification and selection process is reported in Figure 22. Table 13 Studies included in the systematic review of economic evaluations. Studies excluded at full text are reported in Table 45 with reasons for exclusion. We identified seven evaluations (in eight reports). The review (in particular the studies by Noon and Montgomery),[111, 112] and review of NICE TAs, highlighted that DES, rather the Markov multistate modelling, is a suitable way to model disease progression for cost-effectiveness analysis in RRMS.

Figure 22 PRISMA flowchart for systematic review of economic evaluations

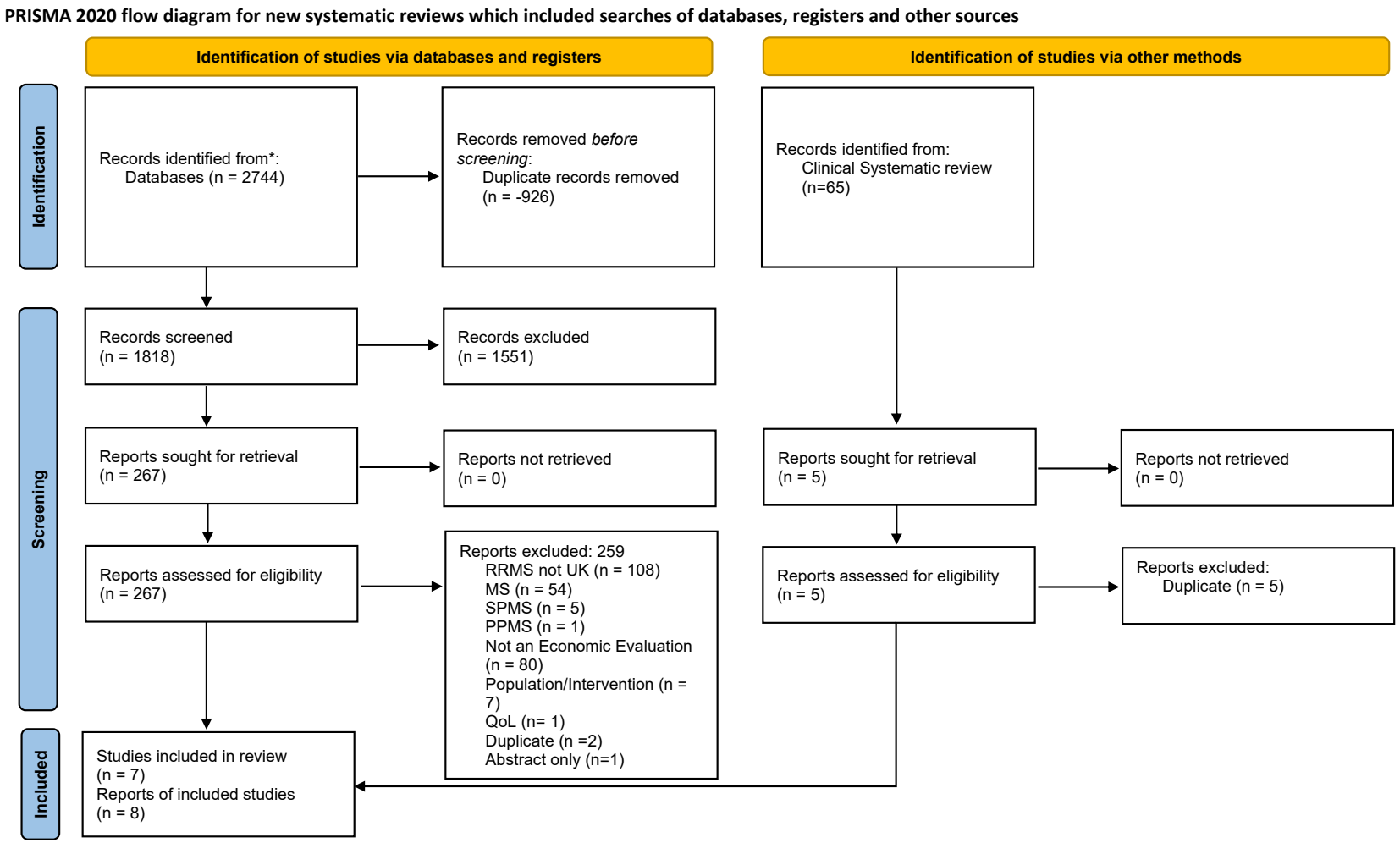


Table 13 Studies included in the systematic review of economic evaluations

Study	Aim	Model type and perspective	Population	Data inputs	Time horizon and discount
Spelman[113]	To evaluate clinical and cost-effectiveness of natalizumab and fingolimod	Markov Model (annual cycle length). NHS perspective.	Adults (>18) with RES - RRMS (≥2 relapses in prior year) starting treatment with natalizumab, fingolimod, or BRACETD, or were previously naïve to DMTs or treated with a different BRACETD.	Clinical IPD from MSBase Registry[114] • ARR • TtfR • CDW6M • CDI6M Costs UK MS burden of illness study[115] • Annualised acquisition, administration and monitoring (UK list price). • Direct and indirect (edss0-9) • Relapse (direct). • Adverse Events. Utilities UK MS burden of illness study[113] • RRMS (EDSS 0-9) • SPMS (EDSS 0-9) • Caregiver • Relapse • Adverse events	Lifetime Horizon. Discount Rate:3.5%
Noon[111]	To investigate the impact of economic model type on the cost-effectiveness of disease-modifying therapies (DMTs) for RRMS.	Markov and discrete event simulation (DES) models. UK payer perspective.	Adults 18-55 with HA RRMS or RES RRMS, >1 relapse in year prior and EDSS 0-5.5. (FREEDOMS[74], FREEDOMS II[116] and TRANSFORMS[75])	Clinical Natural History data from placebo arm of FREEDOMS and FREEDOMS II. EDSS >8 calculated based on London Ontario dataset.[117] • ARR Costs • Drug costs based on list price (without discount).	Markov: baseline cohort age + 50 yrs and DES: tracked each simulated patient until death (capped at 100 yrs). Discount Rate 3.5%.

Study	Aim	Model type and perspective	Population	Data inputs	Time horizon and discount
				• Resource use (administration, monitoring, AEs and drug acquisition) • Relapses (NHS National Tarif) (Costs and QALYs calculated in annual cycles with ½ cycle correction in the Markov and applied on a continuous-time basis in the DES) <u>Utilities</u> • EQ-5D • EDSS • Disutilities associated with AEs were matched across models (adverse events, retreatment).	
Hettle[118]	To assess the cost-effectiveness of cladribine tablets in HDA-RRMS compared with alemtuzumab and natalizumab	Markov (annual cycle length). NHS Perspective	Adults with RRMS, >1 relapse within 12 months, and EDSS <5.5. Based on CLARITY[86]	<u>Clinical</u> Natural History reference model using data on disability and relapse for people receiving Best Supportive Care and treatment-adjusted model combing the Natural History model with comparative efficacy and safety of treatment vs placebo.[119] • 6-months confirmed disability progression • ARR <u>Costs</u> • Drug acquisition, administration and monitoring based on list price (without discount). • Annualised direct medical costs taken from Hawton and Green[120] <u>Utilities</u>	50 year horizon. 3.5% discount.

Study	Aim	Model type and perspective	Population	Data inputs	Time horizon and discount
				• EDSS from CLAIRTY trial[86] • Health State Utilities from Hawton and Green.[120] • EDSS-related utility loss for caregivers.	
Melendez-Torres[121]	HTA to determine effectiveness and cost effectiveness of beta-interferon and glatiramer acetate for RRMS/SPMS.	Markov (annual cycle length). NHS and Personal and Social Services (PSS)	RRMS patients	<u>Clinical</u> Systematic Review and Natural History from British Columbia Multiple Sclerosis database (closed since 2009) <u>Costs</u> Systematic review and[122] • Resource use • Unit costs Utilities MS Trust surveys • EQ-5D converted to EQ-5D index score.	50 year horizon. 3.5% discount.
Palace[123]	To assess the long-term effectiveness and cost-effectiveness of interferon beta and glatiramer acetate.	Markov and a multilevel model (to model treatments in the RSS)	Adults >18 with 2 significant relapses in prior 2 yrs and EDSS >5.5.	Clinical UK RSS clinical cohort compared to the BCMS database. • accumulation of disability measured as EDSS progression and loss of utility.	20 years. 3.5% discount.
Herring[124]	To estimate the comparative effectiveness of switching to natalizumab or fingolimod or within BRACETD using real-world data and to	Markov. UK NHS.	Adults with HA RRMS with inadequate response after >1 year on first line DMT who switched to natalizumab, fingolimod, or another BRACETD.	Clinical MSBase Registry and published trials. Costs/utilities: 2015 UK MS burden of illness survey used to estimate indirect costs and utility values.	Lifetime. 3.5% discount.

Study	Aim	Model type and perspective	Population	Data inputs	Time horizon and discount
	evaluate the cost-effectiveness of switching to natalizumab versus fingolimod using a United Kingdom (UK) third-party payer perspective.		Primary endpoint: change in EDSS.	treatment costs were list price and standard UK costs.	
Montgomery[112, 125] (1 study in two eligible reports)	to model IPD from key trials in DES for the cost-effectiveness analysis of the treatments fingolimod and alemtuzumab recommended by NICE for use in HA RRMS patients,	DES model in C++. NHS and Personal and Social Services (PSS)	Adults 18-55 with RRMS, >1 relapse in year prior and EDSS 0-5.5. (from from FREEDOMS, FREEDOMS II and TRANSFORMS)	<u>Clinical</u> • IPD from placebo arms of HARRMS subgroup of the Key trials; FREEDOMS, FREEDOMS II and TRANSFORMS for EDSS 0-7 supplemented with data from London Ontario for EDSS >8.[17] • ARR, AEs from FREEDOMS, FREEDOMS II and TRANSFORMS. <u>Costs</u> • Drug acquisition based list price (no discount) • Treatment acquisition, administration and monitoring. • Relapse cost from NGS National Tariff • EDSS costs from previous NICE submissions[21] Utilities • EQ-5D • Disutitlties based on [9,17,21,13]	Life time horizon (capped at 100). Primary output: Costs and QALYS discounted at 3.5%. ICER and NMB.

AAR: annualized relapse rate; CDI3M: time to 3-month–confirmed disability improvement; CDI6M: time to 6-month–confirmed disability improvement; CDW3M: 3-month–confirmed disability worsening; CDW6M: 6-month–confirmed disability worsening; DES: Discrete simulation model; EDSS: Expanded Disability Status Scale; IPD: Individual Patient Data; MS: Multiple Sclerosis; QoL: Quality of Life; RES-RMMS: Rapidly Evolving Severe Relapsing-Remitting Multiple Sclerosis; RSS: Risk Sharing Scheme; SPMS: Secondary Progressive Multiple Sclerosis; SRRMS: Relapsing-Remitting Multiple Sclerosis; TtfR: time to first relapse.

6.2 Independent economic assessment

An economic model was developed to compare the cost-effectiveness of treatments for HARRMS after at least one disease modifying therapy.

The target population for our economic evaluation was people with HARRMS who have received at least one previous DMT. As the evidence on this population is limited, we used evidence in any RRMS (including studies with at least 90% of participants with RRMS) to fill any gaps.

The interventions were Natalizumab (Tysabri), delivered subcutaneously or intravenously, and intravenous natalizumab biosimilar (Tyruko). Comparators are aligned with those of the overall appraisal (Table 4):

- Glatiramer acetate
- Interferon beta 1a
- Interferon beta 1b
- Alemtuzumab
- Cladribine tablets
- Fingolimod
- Ocrelizumab
- Ofatumumab
- Ponesimod
- Autologous haematopoietic stem cell transplantation

Only comparators with efficacy and safety data, as identified by the clinical SLR, necessary for the economic model were assessed. There was no clinical evidence identified on autologous haematopoietic stem cell transplantation so this was not included in the economic model.

We aligned with recommendations of the NICE reference case. We therefore took an NHS and NHS and personal and social services (PSS) perspective and lifetime horizon. Health benefits were measured using Quality Adjusted Life Years (QALYs). Discounting was applied to both costs and benefits at the annual 3.5% rate.

The model and cost-effectiveness analysis were fully probabilistic with any specific parameter or structural sensitivity analyses also probabilistic.[126, 127]

6.3 Models used in relevant TAs

We reviewed the economic models used in relevant NICE TAs. These were the TAs for natalizumab and the comparators listed in Table 3 that were categorised as "Recommended for RRMS in specific situations or specific subtypes" or "Recommended for previously treated RRMS" in Table 3. TAs were identified by informally searching the NICE website and supplemented by any additional assessments identified by the cost-effectiveness review of Section 6.1.

6.3.1 TA767 Ponesimod

TA767 2022[42] assessed the cost-effectiveness of Ponesimod (Ponvory, Janssen) for RRMS at first or second line. The Markov model simulates a cohort of patients over a lifetime progressing through 10 RRMS & 10 SPMS EDSS health states leading up to death. The natural history of disability progression for RRMS patients was based on the British Columbia Multiple Sclerosis registry.[128] Annual relapse rates by disability[129] were based on population data from the burden of illness 2005 UK MS Survey[130] and patient data from a prospective study.[131] Conversion from RRMS to SPMS was based on data from the London Ontario MS database.[129] The placebo arm of the AFFIRM trial was used to modify the natural history for the HA RRMS subgroup.[34]

The model inputs for patients on treatment with Ponesimod were reported by OPTIMUM & OPTIMUM-LT trials. The CDP-3 & CDP-6 outcomes modify disability progression, the ARR to estimate the number of relapses, and the proportion experiencing AEs. The model accounts for treatment waning, discontinuation, and excess mortality due to MS. Health state costs[132] and utilities[130] were included. Disutilities were applied for disability, relapse, AEs, and caregivers. The External Assessment Group (EAG) was critical of the model not allowing for treatment switching or sequencing and considered this to be an oversimplification of clinical practice, they acknowledged limitations maybe due to the availability of data.

6.3.2 TA699 Ofatumumab

TA699 2021[41] assessed the cost-effectiveness of Ofatumumab (Kesimpta, Novartis) for RRMS at first or second line. The Markov model simulates a cohort of patients over a lifetime progressing through 10 RRMS & 10 SPMS EDSS health states leading up to death. The natural history of disability progression for RRMS patients was based on the British Columbia Multiple Sclerosis registry.[128] Annual relapse rates by disability[129] were based on population data from the burden of illness 2005 UK MS Survey[130] and patient data from a prospective study.[131] Conversion from RRMS to SPMS was based on data from the London Ontario MS database[129] supplemented by data from the EXPAND trial. The HA RRMS subgroup was modelled but not considered suitable for decision making.

The model inputs for patients on treatment with Ofatumumab were reported by ASCLEPIOS I & II trials. The CDP-3 & CDP-6 outcomes modify disability progression, the ARR to estimate the number of relapses, the proportion experiencing AEs, and quality of life data. The model accounts for treatment discontinuation, and excess mortality due to MS. Health state costs were included,[132] and disutilities were applied for disability, relapse, AEs, and caregivers. The EAG was critical of the model not having incorporated loss of treatment effectiveness, they accepted treatment discontinuation as a proxy to waning as in TA533.

6.3.3 TA616 Cladribine

TA616 2019[38] assessed the cost-effectiveness of Cladribine tablets (Mavenclad, Merck Serono) for RES RRMS at first or second line and HA RRMS (SOT RRMS) at second line. The Markov model simulates a cohort of patients over a lifetime progressing through 10 RRMS leading up to death. The natural history of disability progression for RRMS patients from the British Columbia Multiple Sclerosis registry[128] adjusted to account for higher probability of progression on the RES and SOT subgroups using CDP-6 from CLARITY.

The model inputs for patients on treatment with Cladribine tablets were from an NMA and Meta-regression that included the key trials CLATIRY & CLARITY-EXT. The CDP-3 & CDP-6 outcomes modify disability progression, the ARR to estimate the number of relapses, the proportion experiencing AEs and quality of life data. The model accounts for treatment discontinuation, and excess mortality due to MS. Health state costs[120, 132, 133] and utilities were included,[120, 130] and disutilities were applied for disability, relapse, AEs, and caregivers. The EAG was critical of the company assuming loss of treatment effectiveness to be delayed for Cladribine tablets, equal treatment effectiveness waning was applied across all comparators.

6.3.4 TA533 Ocrelizumab

TA533 2018[33] assessed the cost-effectiveness of Ocrelizumab (Ocrevus, Roche) for RRMS at first or second line. The multi—state Markov model simulates a cohort of patients over a lifetime progressing through 20 RRMS & 10 SPMS EDSS health states leading up to death. The natural history of disability progression for RRMS patients was based on the British Columbia Multiple Sclerosis registry.[128] Annual relapse rates by disability were based on population data from the burden of illness 2005 UK MS Survey[130] and patent data from a prospective study.[131] Conversion from RRMS to SPMS was based on data from the London Ontario MS database.[129] The placebo arm of the AFFIRM trial was used to modify the natural history for the HA RRMS subgroup.

The model inputs for patients on treatment with Ocrelizumab were reported by OPERA I & II trials. The CDP-3 & CDP-6 outcomes modify disability progression, the ARR to estimate the number of relapses, the proportion experiencing AEs and quality of life data. The model accounts for treatment discontinuation, and excess mortality due to MS. Health state costs were included,[132] and disutilities were applied for disability, relapse, AEs, and caregivers. The EAG was critical of the model not having incorporated loss of treatment effectiveness which in clinical practice would lead to patients switching on to other treatments, they accepted treatment discontinuation as a proxy.

6.3.5 TA312 Alemtuzumab

TA312 2014[39] assessed the cost-effectiveness of Alemtuzumab (Lemtrada, Sanofi) for Active RRMS at first line RES RRMS at first or second line and HA RRMS at second line. The multi-state Markov model simulates a cohort of patients over a lifetime progressing through 10 RRMS & 9 SPMS EDSS health states leading up to death. The natural history of disability progression for RRMS patients and converting to SPMS states was based on the London Ontario MS database.[129] Annual relapse rates by disability were based on population data from the burden of illness UK MS Survey[130] and patent data from two prospective studies.[131, 134]

The model inputs for patients on treatment with Alemtuzumab were from an NMAs specific to the RRMS and RES RRMS and HA RRMS subgroups that included the key trials CAMMS223, CARE-MS I & II. The Sustained Accumulation of Disability (SAD-3 & SAD-6) outcomes modify disability progression, the ARR to estimate the number of relapses, the proportion experiencing AEs and quality of life data. The model accounts for treatment discontinuation, and excess mortality due to MS. Health state costs,[132, 133, 135] were included and disutilities were applied for disability, relapse, AEs, and caregivers. The EAG was critical

of the company assuming no loss of treatment effectiveness for Alemtuzumab, clinical advice was that patients would be offered alternative treatments after discontinuation but as treatment switching was not implemented in the model, the committee concluded it was appropriate to model long-term treatment waning.

6.3.6 TA254 Fingolimod

TA254 2012[40] assessed the cost-effectiveness of Fingolimod (Gilenya, Novartis) for HA RRMS at second line. The Markov model simulates a cohort of patients over a lifetime progressing through 10 RRMS & 10 SPMS EDSS health states leading up to death. The natural history of disability progression for RRMS patients and converting to SPMS states was based on the London Ontario MS database.[117] Annual relapse rates by disability were based on population data from the burden of illness UK MS Survey[130] and patient data from a prospective study.[131]

The model inputs for patients on treatment with Fingolimod versus Avonex were reported on the TRANSFORMS & FREEDOMS trials. An NMA was undertaken to estimate relative treatment effects of other beta interferons. The SAD-3 & SAD-6 outcomes modify disability progression, the ARR to estimate the number of relapses, the proportion experiencing AEs. The model accounts for treatment discontinuation, and excess mortality due to MS. Health state costs,[34] utilities[130], were included and disutilities were applied for disability, relapse, AEs, and caregivers. The model has many limitations which were critiqued by the EAG and are summarised in Table 98, they called for a new decision model, one that better reflects clinical practice in future appraisals of Multiple Sclerosis.

6.3.7 TA127 Natalizumab

TA127 2007[34] assessed the cost-effectiveness of Natalizumab (Tysabri, Biogen Idec) for RES RRMS at first or second line. The multi-state Markov model simulates a cohort of patients over a lifetime progressing through 10 RRMS & 10 SPMS EDSS health states leading up to death. The natural history of disability progression for RRMS patients and converting to SPMS states was based on the London Ontario MS database.[117] Annual relapse rates by disability were based on population data from the burden of illness UK MS Survey[130] and patient data from a prospective study.[131] The placebo arm of the AFFIRM trial was used to modify the natural history for the HA RRMS subgroup.

The model inputs were obtained from a number of sources. The Hazard ratios for disability progression and annual relapse of RES RRMS patients on treatment with Natalizumab was obtained from the AFFIRM trial and converted to risk ratios. The risk ratios for disability progression and annual relapse for patients on beta interferon or glatiramer acetate were obtained from pairwise meta-analyses, data from two Cochrane reviews.[136, 137] The analyses derived relative treatment effects contrasting the risk ratios from the Intention to Treat (ITT) and RES Natalizumab groups versus either of the beta interferon or glatiramer acetate ITT groups' risk ratios. The risk ratios for disability progression could be multiplied directly with the natural history transition matrices. However, the relapse risk ratios describe had to be transformed into relative relapse rates using the annualised relapse rate from the placebo groups in AFFIRM from the RES RRMS sub group, and the ITT main group as a proxy for the SOT RRMS subgroup. Health state costs and utilities[130], were included and disutilities were applied for disability, relapse, AEs, and caregivers. The ERG was critical of the company

excluding the SENTINEL trial SOT RRMS subgroup data from the model, especially that it was relied on for the marketing authorisation.

6.3.8 Common criticisms

1. Treatment sequencing and variable treatment waning was an issue in all the reviewed submissions (TA767, TA699, TA616, TA533, TA312, TA254 and TA127) to varying degrees. These TAs explain that clinical practice is to switch patients to alternative treatments if their current drug is no longer effective. The ERGs have accepted treatment discontinuation as proxy for loss of effectiveness over time, despite lack of evidence on waning from the key trials. This is because treatment switching was not modelled in any of these submissions.

2. Previous models (TA767) have modelled relative risk of death being applied to each EDSS health state, taken from Pokorski (1997) which demonstrated that risk of death because of multiple sclerosis was primarily dependent on disability. But this dataset is quite old and has been criticised by clinicians for this reason.

3. Previous models in Multiple sclerosis have had limited ability to accurately reflect the course of the condition. In TA767 and TA699 an implausible number of patients were found in high EDSS states contrary to what would be observed in clinical practice. In TA699 and TA127 issues with converting from RRMS to SPMS were discussed. In TA254 and TA127 issues with unrealistic disability progression when treatment effects were applied to the natural history was discussed.

6.4 Model structure

To overcome the key criticisms of the previous manufacturer models for RRMS submitted to NICE (Section 6.3.8), we adopted an individual-level discrete-event simulation (DES) model.[138] This makes it possible to model treatment sequences and enable treatment-specific waning patterns. The inflexibility of cohort Markov models made it difficult to accurately reflect the course of MS, leading to implausible numbers of patients in the high EDSS states.[42] The flexibility of DES better reflects the natural course of MS, and eases the inclusion of new standardised mortality rates by EDSS (TA767).[42, 139]
Our model structure was influenced by the recent Dutch clinical guidelines models on RRMS which was a microsimulation accounting for treatment sequences. [140-143] However, rather than using a DES, this microsimulation used an underlying multistate structure defined by EDSS and SPMS status, similar to the Markov models used in previous NICE submissions (Section 6.3). Our justification for adopting event-based rather than state-based modelling is that the target of RRMS treatment is to reduce the events of relapse and disability progression, rather than to directly affect EDSS severity or SPMS status. A DES is therefore better tailored to RCT data and the focus of RRMS treatment.

The model is illustrated in Figure 23. The attributes of the DES represent important demographic and disease characteristics. The modelled disease characteristics included EDSS ($\in (0, \ldots, 9)$) and SPMS status to thus capture health state information of the previous RRMS Markov models (Section 6.3). Age and gender were modelled as demographic attributes and determine the rate of background mortality. Treatment status was included and described in more detail below.

Event rates depended on some or all of these attributes. If a patient has not yet progressed to SPMS, events included increase in severity (i.e., EDSS increase), decrease in severity (i.e., EDSS reduction), progression to SPMS, relapse, adverse events, treatment change not driven by an event, and death. If a patient has progressed to SPMS, the events included increase in severity (i.e., EDSS increase), relapse, adverse events, and death.

Treatment status is a key attribute, and the sequence of treatment is represented in Figure 24. The initial treatment was any of the interventions/comparators in highly active RRMS. Following this, rescue therapy and later line therapy will follow the currently recommended pathway described in Section 1.3.5. Patients can progress to SPMS on any line of RRMS therapy and are then assumed to receive an average 'basket' of approved therapies, as described in Section 1.3.5.

We resolved competing risks using the "event-specific" approach, which requires sampling times for all competing events and simulating the event that is the first to occur.[144, 145] The alternatives (sampling the event to occur first and then the time-to-event; sampling the time-to-event and then the event) required data to be analysed in a joint manner, which was not possible in this setting as rates of (for example) CDP3/6, ARR, and adverse events were estimated independently.

Progressive Multifocal Leucoencephalopathy (PML) is an important side effect of some MS drugs, particularly natalizumab and its biosimilar.[76, 146] It is caused by suppression of the immune system which can cause the John Cunningham human polyomavirus (JCV), to become active.[146] Biogen, the manufacturer of natalizumab, currently fund JCV testing and report a risk of PML.[147] However, our clinical advice was that this scheme is not widely implemented so the cost of JCV testing was included for natalizumab. Testing is also not routinely done for the biosimilar and would need to be funded by the NHS. We therefore included this JCV virus testing for the biosimilar in the base case .

Figure 23 Model diagram for cost-effectiveness DES model

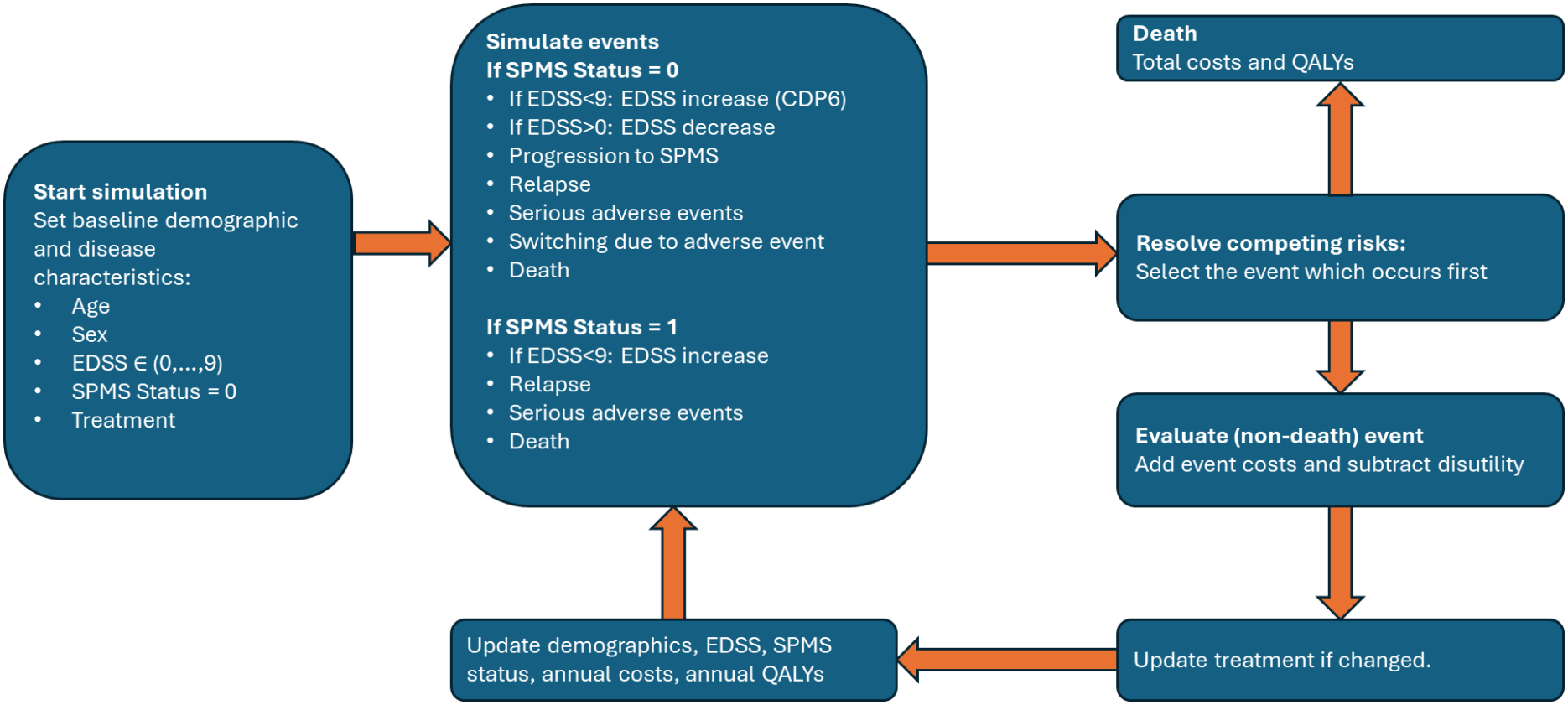
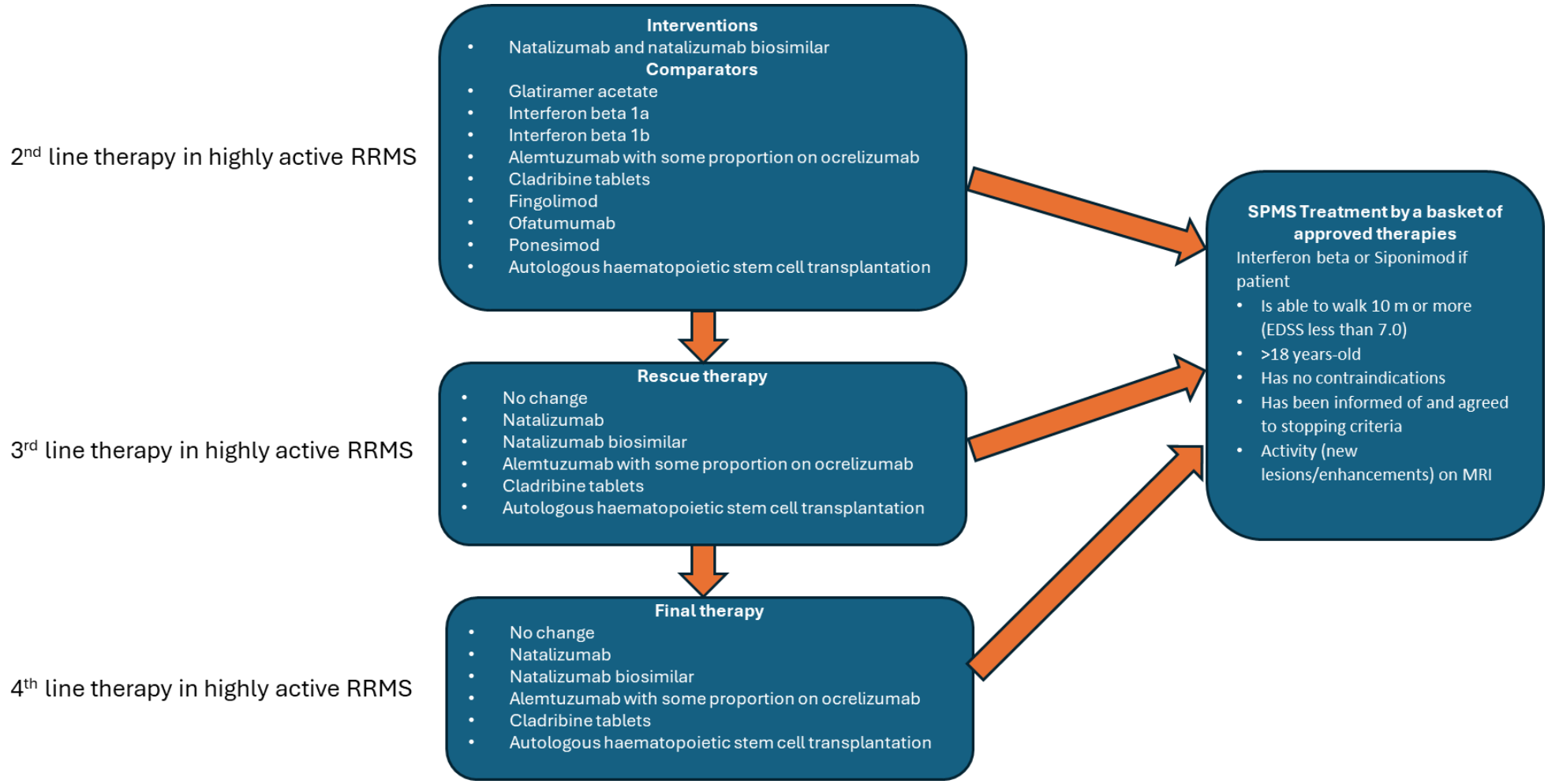


Figure 24 Treatment sequence in the cost-effectiveness DES model*



*Patients modelled on individual therapies from options at 3rd and 4th line, rather than a basket.

6.5 Input data

6.5.1 Clinical outcomes and treatment effects

The event rates were a combination of natural history (informed by analyses of MS registry data described below) and treatment effects. Treatment effects came from the NMA described in Section 4.3.6. Treatment class effects was assumed where relative treatment effects not estimated by NMA. Events for patients with RRMS (i.e., SPMS status = 0) with treatment effects were EDSS increase (i.e., CDP6), relapse (i.e., ARR), serious adverse events, and discontinuation due to adverse events. No treatment effect was assumed for progression to SPMS, EDSS decrease, or mortality. Events for patients with SPMS (i.e., SPMS status = 1) were assumed not to be affected by the RRMS treatment. The natural history data for SPMS patients represents outcomes on the basket of treatments described in Figure 24, and was again informed by MS registry analyses described below.

Proportion of relapses leading to hospitalisation were from observational studies on the costs and utilities of relapses.[120]

Relapse rates in SPMS were informed by the MS registry analyses and were regressed on EDSS severity. Rates were expected to decrease with increasing severity, following EAG recommendations in TA699 and rates reported in TA527.[31, 41] In TA767 For people who progressed to SPMS, people were assumed to transition through health states based on the London Ontario dataset.[42]

Regarding the choice of CDP6 instead of CDP3 to represent EDSS decrease, in TA767 the EAG recommended that CDP6 was a more appropriate measure of disease progression following clinical advice that CDP3 may potentially overestimate progression due to natural fluctuations in the disease.[42] CDP6 was also preferred in other previous appraisals.[39]

Baseline rates of discontinuation due to AEs provided a proxy to waning as in previous appraisals, and were assumed to follow the AFFIRM study for natalizumab and ANTELOPE study for natalizumab biosimilar. For comparators we used the NMA on discontinuation due to AEs (Section 5.1.5**Error! Reference source not found.**) and applied treatment effects to t he baseline rates from AFFIRM.

6.5.2 MS Registry analyses

The following data specification was shared with the MS Registry on 8th August 2024. Analyses are separated into those that are essential and those that are desirable. Published sources will be used in place of those that are desirable but infeasible.

6.5.2.1 Requested analyses

We requested rates of events using exponential survival and continuous-time multistate models fit to interval censored data. Covariates were included in some of these models. Outputs needed were model parameters and their covariance matrices on the natural scale (e.g., log rates for exponential and multistate models). Age and sex were considered as covariates in all models but were removed due to limited data.

The model specification is provided in Table 14.

Unless otherwise specified, analyses were conducted in highly active RRMS, any RRMS, and SPMS. The RRMS populations matched those of the NMA, namely highly active RRMS who have received at least one previous DMT, and any RRMS. As noted in Table 2 there is no consensus definition of highly active RRMS. Previous appraisals for NICE have used different definitions. The MS registry aimed to align as closely as possible with our selected definition: Unchanged or increased clinical or radiological evidence of disease activity despite treatment with at least one DMT.

A covariate effect was included to represent treatment. However we did not use the MS registry to estimate hazard ratios as these come from the NMA based on RCT data. The covariate for treatment is only used to obtain baseline rates specific to natalizumab, to which the NMA hazard ratios were applied. Treatments included are the interventions, noting that that Natalizumab biosimilar (Tyruko) was not included in the registry, and the comparators:

- Natalizumab (Tysabri), delivered subcutaneously or intravenously,
- Glatiramer acetate
- Interferon beta 1a
- Interferon beta 1b
- Alemtuzumab
- Cladribine tablets
- Fingolimod
- Ocrelizumab
- Ofatumumab
- Ponesimod

We requested sample sizes and total exposure times to be reported for all analyses in Table 14 and Table 15.

We furthermore requested the EDSS distribution at baseline so as to inform the starting point for our model.

Table 14 Essential requested analyses in RRMS and Highly Active RRMS.*

Event	Effect estimate	Model	Covariates
EDSS increase (i.e., confirmed disability progression)	Rate	Exponential	Treatment, current EDSS
EDSS decrease	Rate	Exponential	Current EDSS
EDSS increase or decrease	Rates	Multistate model with state for each EDSS category (0, 1, …, 9)	Treatment on EDSS increase only
Relapse	Rate	Exponential	Treatment, current EDSS
Progression to SPMS	Rate	Exponential	Current EDSS

*Rates are required separately in two populations: highly active RRMS who have received at least one previous DMT, any RRMS

Table 15 Essential requested analyses in SPMS.

Event	Effect estimate	Model	Covariates
EDSS increase (i.e., confirmed disability progression)	Rate	Exponential	Current EDSS
EDSS increase or decrease*	Rates	Multistate model with state for each EDSS category (0, 1, …, 9)	
Relapse	Rate	Exponential	Current EDSS

*Not used in model, only for exploration

6.5.3 Utilities

Utilities associated with model attributes (EDSS and SPMS status) were derived from previous appraisals and the SLR on cost-effectiveness evidence (Section 6.1). Disutilities for events (i.e., relapse, adverse events) were also derived from these sources.

The base case utilities are from the UK MS Survey 2005, a cross-sectional study of MS patients (n=2048) with self-reported EQ-5D quality of life and resource use via a postal questionnaire.[130] The authors report the questionnaire was adapted from a descriptive cost of illness study conducted in the UK in 1999 by Kobelt et al[148] the design of which closely follows a cross-sectional study in Sweden by Henriksson et al.[149]

Unlike the studies by Kobelt et al or Henriksson et al, the UK MS Survey patients were self-reporting and had not been assessed in clinic. Disease severity was self-assessed on the Adapted Patient Determined Disease Steps (APDDS) scale but reported by Expanded Disability Scale (EDSS) strata, these scales are used interchangeably by authors although they do not cite evidence in support of this assumption.[150] The distribution of patient characteristics were reported grouped by APDSS 0-3 (21%) APDSS 4-6.5 (60%) and APDSS 7-9.5 (19%).

Multivariate linear regression analysis was used to fit an ANOVA model, and authors reported mean (95% CI) utility stratified by APDSS, relapse, SPMS, PPMS, education (college, university, postgraduate), sex and years since diagnosis. The presented model has moderate explanatory power (R^2=0.478), alternative models were not available. The uncertainty in the estimates for the 11 stratified severity states is such that confidence intervals overlap with each other.

The UK MS Survey 2005 was the source of utility values in TA767, TA699, TA533, TA312, TA254, and TA127. A variation of these utility values were reproduced in TA127 with slightly higher mean estimates by excluding the education variables. Furthermore, disutility of relapse was stratified by severity using data from the AFFIRM trial. Uncertainty was not reported for this analysis, limiting its applicability for our fully probabilistic model.

Trial utilities stratified by severity were used in TA533 by pooling both treatment and placebo arms of OPERA I & II (EDSS 0-5) and combined with Orme et al. (EDSS 6-9). They were used in TA616 by pooling both treatment and placebo arms of CLARITY & CLARITY-EXT (EDSS 0-5) and combined with Hawton et al (EDSS6-8) and Orme et al (EDSS 9) as shown in Table 17. Trial utilities were redacted from TA696 (ASCLEPIOS), TA254 (TRAMSFORMS & FREEDOMS).

A systematic review of utilities in MS identified 16 studies reporting utilities associated with health states in MS as measured by EDSS, 3 of these were UK studies.[151] The manufacturer in TA624 and the ERG in TA767 ran scenarios using the utilities reported in a study by Thompson et al. That data was from the study by Kolbet et al and utility values are broadly similar to Orme. Uncertainty was again not reported for this analysis, limiting its applicability for our fully probabilistic model.

The committee in TA254 preferred utility data from Orme was combined with utility data from key trials. The TA533 committee thought utilities for the rapidly evolving severe subgroup were over estimated.

Table 16 Health state and relapse utilities used in economic model as calculated from the UK MS Survey 2005

	RRMS		SPMS	
	Mean	**sd**	**Mean**	**sd**
EDSS0	0.870	0.045	0.825	0.061
EDSS1	0.799	0.093	0.754	0.109
EDSS2	0.705	0.093	0.660	0.108
EDSS3	0.574	0.097	0.529	0.113
EDSS4	0.610	0.093	0.565	0.108
EDSS5	0.518	0.092	0.473	0.108
EDSS6	0.458	0.092	0.413	0.108
EDSS7	0.297	0.094	0.252	0.110
EDSS8	-0.049	0.095	-0.094	0.111
EDSS9	-0.195	0.119	-0.240	0.135
	Mean		**sd**	
Relapse	-0.071		0.016	
Years since diagnosis	0.002		0.001	

Table 17 Health State utility values stratified by severity for RRMS patients. UK MS Survey 2005 model formula and pooled estimates from key trials.

	UK MS Survey 2005			OPERA		CLARITY	
	Mean	**LCI**	**UCI**	**Mean**	**SD**	**Mean**	**SD**
EDSS0	0.87	0.782	0.958	0.8809	0.0154	0.906	0.026
EDSS1	-0.071	-0.165	0.023	0.8438	0.0071	0.845	0.046
EDSS2	-0.165	-0.259	-0.072	0.7699	0.0061	0.804	0.012
EDSS3	-0.296	-0.398	-0.195	0.7048	0.0069	0.701	0.701
EDSS4	-0.26	-0.354	-0.167	0.6438	0.0087	0.655	0.013
EDSS5	-0.352	-0.444	-0.26	0.6003	0.0130	0.565	0.026
EDSS6	-0.412	-0.505	-0.319	0.4909	0.0204	0.573	0.225
EDSS6.5	-0.408	-0.502	-0.314	-	-	-	-
EDSS7	-0.573	-0.67	-0.477	0.4387	0.0990	-	-
EDSS8	-0.919	-1.017	-0.82	-	-	-	-
EDSS9	-1.065	-1.21	-0.919	-	-	-	-
Recent relapse‡	-0.071	-0.096	-0.046	-0.1006	0.0201	-	-
SPMS	-0.045	-0.076	-0.014	-	-	-	-
Years since diagnosis	0.002	0.001	0.003	-	-	-	-

‡binary variable indicating presence or absence of relapse in the past 3 months.

Carer disutilities for our base case used data from a commonly cited study. This online survey of 200 caregivers by Acaster et al, matched care givers (n=200) with controls from the general population asked (n=400).[152] Respondents self-reported EQ-5D, SF-36 and HADS, MS Disease severity was stratified for using the self-reported PDSS. Authors report significant differences between cases and controls as measured on the SF-36 scale and HADS but the results for EQ-5D uncertain. The manufacturer of Natalizumab utilized caregiver disutilities for patients suffering from Alzheimer's disease in their 2008 submission for TA127.[153]

Table 18 Carer disutilities

	TA127		Acaster et al	
	Mean	SE	Mean	SE
EDSS0	0.000	0.000	-0.002	0.053
EDSS1	-0.001	0.000	-0.002	0.053
EDSS2	-0.003	0.001	-0.045	0.057
EDSS3	-0.009	0.002	-0.045	0.057
EDSS4	-0.009	0.002	-0.142	0.062
EDSS5	-0.020	0.004	-0.16	0.055
EDSS6	-0.027	0.005	-0.173	0.054
EDSS7	-0.053	0.011	-0.03	0.038
EDSS8	-0.107	0.021	-0.095	0.075
EDSS9	-0.140	0.028	-‡	-

‡ we assumed these to be the same as EDSS8

Serious Adverse Events utility decrements are assumed to be a single Natalizumab specific utility decrement that was calculated as a weighted average of those reported in the AFFIRM trial.[77] The proportion of patients experiencing PML was provided by Biogen[154] using data from the 15 year final Analysis of the TOP study for the global population (n=6321) treated with Natalizumab.[155] The annual utility decrements associated with Serious AEs for Natalizumab have been reported in previous RRMS appraisals as outlined in Table 19.

Table 19 Serious Adverse Events utility decrements assumed for treatments in the model based on the AFFIRM trial

Serious Adverse Events	Utility decrement (annual)	Duration (days)	Utility decrement (per event)	source
Urinary tract infection	-0.10	5	-0.0014	TA767, TA699
Depression	-0.56	365.25	-0.5600	TA699
Anaphylactic reaction	-1.00	7	-0.0192	TA312
Hypersensitivity reaction	-1.00	7	-0.0192	TA616
Breast cancer	-0.1160	365.25	-0.1160	TA616
PML	-0.30	365.25	-0.3000	TA767, TA699

6.5.4 Costs and resource use

Drug costs were derived from previous appraisals, the SLR on economic evidence described in Section 6.1, and PAS prices provided by NICE. Event costs were derived from previous appraisals and the SLR.

The categories of costs utilized in the economic model include: drug acquisition, drug administration, drug monitoring and serious adverse events costs obtained from the BNF and manufacturer submissions. Health state and relapse costs were obtained from analyses of observational studies widely used in previous submissions. These are assumed to be from a NHS and PSS perspective, unless otherwise stated. Where necessary, costs were inflated to the financial year 2022/2023.

The annual drug acquisition costs are in line with the costs of Natalizumab, Natalizumab bio similar, Ofatumumab and Ocrelizumab reported in the Sandoz submission. The number of annual doses for Natalizumab are in line with those reported in the Biogen submission. The annual number of units prescribed and annual costs were reported in MS single and multiple technology appraisals. We cross referenced list prices with the BNF and the annual units prescribed with our clinical advisors. Annual drug acquisition costs and proportions of patients treated beyond year two are detailed in Table 20. List drug prices for some generics are detailed in Table 26.

Table 20 Annual Treatment acquisition (list prices) quantities, costs and proportion of patients retreated.

Treatment	**Year 1**		**Year 2 onwards**		**Patients re-treated (percentage)‡**		
	Units (n)	**Cost (£)**	**Units (n)**	**Cost (£)**	**Year 3**	**Year 4**	**Year 5+**
Ponesimod 20 mg	1 daily	£14,010	1 daily	£14,010	75%	75%	75%
Ofatumumab 20 mg	15	£22,388	15	£17,910	95%	95%	95%
Alemtuzumab 12 mg	5	£35,225	3	£21,135	40%	0%	0%
Cladribine Tablets	12.67	£25,953	12.67	£25,953	25%	25%	0%
Ocrelizumab300 mg	4	£19,160	4	£19,160	95%	95%	95%
Fingolimod500 µg	1 daily	£19,176	daily	£19,169	75%	75%	75%
Natalizumab-IV300 mg	13	£14,690	13	£14,690	80%	80%	80%
Natalizumab-SC 300 mg	13	£14,690	13	£14,690	80%	80%	80%
Natalizumab-IV-biosimilar 300 mg	13	£13,221	13	£13,221	80%	80%	80%
Peginterferon -β-1a SC 125µg	1 bi-weekly	£8,502	1 bi-weekly	£8,502	50%	50%	50%
Interferon-beta-1a SC 44µg	3 weekly	£10,311	3 weekly	£10,311	50%	50%	50%
Interferon-beta-1a SC 22µg	3 weekly	£7,976	3 weekly	£7,976	50%	50%	50%
Interferon-beta-1a IM 30µg	1 weekly	£8,502	1 weekly	£8,502	50%	50%	50%
Interferon-beta-1b SC 250µg	1 every other day	£7,239	1 every other day	£7,239	50%	50%	50%
Glatiramer acetate SC 20 mg	1 daily	£6,681	1 daily	£6,681	50%	50%	50%

Treatment	Year 1		Year 2 onwards		Patients re-treated (percentage)‡		
	Units (n)	Cost (£)	Units (n)	Cost (£)	Year 3	Year 4	Year 5+
Glatiramer acetate SC 40 mg	1 daily	£6,681	1 daily	£6,681	50%	50%	50%
Patients progressing on to SPMS assumed to be treated with an annual cost for the remaining duration.							
Siponimod	£ 7,239				1		
Peginterferon -β-1a SC 125µg	£8,502				1		

‡100% of patients treated in years 1 and 2 with some patients needing retreatment years 3, 4, 5+.

Administration Costs

In previous technology appraisals treatment administration visits were classed as neurology outpatient visit by the manufacturers of Natalizumab-IV,[34] and Fingolimod.[40] Classed as day case (admitted patient care) by the manufacturers of Alemtuzumab,[39] Ocrelizumab,[33] further includes comparators Natalizumab-IV and Fingolimod in manufacturers' submissions.[33, 38-41]

Our clinical advisors agreed that all treatment administration visits are day cases. The HRG grouper code AA30# used to cost day cases,[33, 34, 39] arises out of group of procedures/interventions/diagnoses (IC-10 codes). The exact AA30# is dependent the on the complication and comorbidity (CC) diagnosis for each individual admitted patient.[156] We have assumed that treatment administration visits for Natalizumab-IV, Natalizumab-SC Alemtuzumab and Ocrelizumab require day cases with frequency of visits determined by number of doses.

The manufacturers anticipate cost savings associated with the administration and monitoring of Natalizumab Sub Cutaneous (SC) in comparison to the intravenous (IV) deliver. However, our clinical advisors explained that in practice patients do not see differences between SC and IV in intensity of resource use. Beta interferons and Ofatumumab are self-administered injections requiring nurses' time to train patients. Tablets; Ponesimod, Cladribine do not require administration day cases with exception of Fingolimod. The detailed administration costs are outline in Table 21

Treatment monitoring visits are required for all treatments which we have assumed to be nurse led outpatient visits. Furthermore, the clinical Advisors pointed out annual MRI monitoring should be undertaken for all treatments and are increasingly routine for Natalizumab and B cell therapies. Monitoring Costs were not included in either of the Sandoz or Biogen submissions, so we have relied on previously published estimates supplemented by clinical advice and updated unit costs. The detailed monitoring costs are in Table 22.

Patients progressing on to SPMS are treated with beta-interforon or Siponimod. The annual treatment administration and monitoring cost of £733 was reported in TA656.[30]

Table 21 Annual Treatment Administration Costs

Treatment	Year 1		Year 2 onwards		Source
	Resource Use	Cost	Resource Use	Cost	
Ponesimod	redacted	£139	redacted	£0.00	TA767[42]
Ofatumumab	3 hours of nurse time (Band 7) [34] (£68)	£204	None [34]	£0.00	PSSRU[157] Sandoz [34]
Cladribine Tablets	None	£0.00	None	£0.00	TA616[38]
Alemtuzumab	5 x day case (£626.13)	£3,130.65	3 x day case (£626.13)	£1,878.39	AA30F Medical care of patients with multiple sclerosis, with CC score 0-1. Day case.[158]
Ocrelizumab	3 x day case (£626.13)	£1,878.39	2 x day case (£626.13)	£1,252.26	AA30F Medical care of patients with multiple sclerosis, with CC score 0-1. Day case[158]
Fingolimod	1 x day case	£626.13	None[40]	£0.00	AA30F Medical care of patients with multiple sclerosis, with CC score 0-1. Day case
Natalizumab – biosimilar-IV Natalizumab-SC	13 x day case (£626.13)	£8,139.69	13 x day case (£626.13)	£8,139.69	AA30F Medical care of patients with multiple sclerosis, with CC score 0-1. Day case[158]
Peginterferon -β-1a SC 25µg Interferon-beta-1a SC 44µg Interferon-beta-1a SC 22µg Interferon-beta-1a IM 30µg Interferon-beta-1b SC 250µg Glatiramer acetate SC 20 mg Glatiramer acetate SC 40 mg	3 hours of nurse time (Band 7)[121]	£204	None[121]	£0.00	PSSRU[157]

Table 22 Annual Treatment Monitoring Costs

Treatment	Year 1		Year 2 onwards		Source
	Resource Use	Cost	Resource Use	Cost	
Ponesimod*	Redacted (£290.20) 1x MRI scan (£334) 0.2 x cardiac day case (£607.29)	£746	Redacted (£228.20) 1x MRI scan (£334) 0.2 x cardiac day case (£607.29)	£684	TA767[42] EB14E Daycase Other Acquired Cardiac Conditions with CC Score 0-2.[38] RD07Z Magnetic Resonance Imaging Scan Requiring Extensive Patient Repositioning[158]
Ofatumumab*	Redacted (£371.11) 1x MRI scan (£334)	£705	Redacted (£306.07) 1x MRI scan (£334)	£641	TA699[41] RD07Z Magnetic Resonance Imaging Scan Requiring Extensive Patient Repositioning[158]
Cladribine Tablets‡	1x neurology (NCL) first visit (£195.74) 2x neurology (NCL) follow up visits (£184.23) 1x MRI scan (£334) 3x Full blood count (£3.37) 1x tuberculin skin test(£60) 1x HBV test(£59)[159] 1x HCV Test(£65)[160]	£1,092	3x neurology (NCL) follow up visits (£184.23) 3x Full blood count (£3.37) 1x HBV test(£59)[159] 1x HCV Test(£65)[160]	£1,021	TA616[38] Consultant Led (CL) / Non-Consultant Led (NCL) 400 Neurology Service WF01B/C Non-Admitted Face-to-Face Attendance, First / Follow-up[158] Pathology services, DAPS04 Clinical biochemistry[158] Multistix 10sg (£41.12 for 100)[161] RD07Z Magnetic Resonance Imaging Scan Requiring Extensive Patient Repositioning[158]
Alemtuzumab	1x neurology (NCL) first visit (£195.74) 11x neurology (NCL) follow up visits (£184.23) 12x bio-chemistry test (£1.55) 12x Full blood count (£3.37) 12x Urinalysis (£8.53) 4 x Thyroid function test (£6.48) 1x H. Papilloma V. Test (£85) 1x Tuberculin skin test (£60)[162] 1 x MRI scan (£334)	£2,889	12x neurology (NCL) follow up visits (£184.23) 12x bio-chemistry test (£1.55) 12x Full blood count (£3.37) 12x Urinalysis (£8.53) 4 x Thyroid function test (£6.48) 1x H. Papilloma V. Test (£85) 1 x MRI scan (£334)	£2,817	NCL 400 Neurology Service WF01A/B Non-Admitted Face-to-Face Attendance, First / Follow-up[158] Pathology services, DAPS04 Clinical biochemistry, DAPS05 Haematology, DAPS07 Microbiology[158] Multistix 10sg (£41.12 for 100)[161] RD07Z Magnetic Resonance Imaging Scan Requiring Extensive Patient Repositioning[158] HPV test, Tuberculin skin test.[39, 163]

Treatment	Year 1		Year 2 onwards		Source
	Resource Use	Cost	Resource Use	Cost	
Ocrelizumab	1x neurology (NCL) first visit (£195.74) 2x neurology (NCL) follow up visits (£184.23) 2x Full blood count (£3.37) 1x liver function (£3.35) 1x varicella zoster virus test (£45)[164] 1 x MRI scan (£334)	£908	3x neurology (NCL) follow up visits (£184.23) 2x Full blood count (£3.37) 1 x MRI scan (£334)	£893	NCL 400 Neurology Service WF01B/C Non-Admitted Face-to-Face Attendance, First / Follow-up[158] Pathology services, DAPS05 Haematology[158] RD07Z Magnetic Resonance Imaging Scan Requiring Extensive Patient Repositioning[158]
Fingolimod	1x neurology (NCL) first visit (£195.74) 3x neurology (NCL) follow up visits (£184.23) 4x Full blood count (£3.37) 4x liver function (£3.35) 2x basic metabolism (£3.35) 0.69x pregnancy test (£3.5) 1x varicella zoster virus test (£45)[164] 0.2x hospitalization (£11,969.84) 1x Ophthalmology (NCL) first visit (£155.06) 1x follow-up Ophthalmology (NCL) visit (£105.46) 1 x MRI scan (£334)	£3,719	2x neurology (NCL) follow up visit (£184.23) 2x Full blood count (£3.37) 2x liver function (£3.35) 2x basic metabolism (£3.35) 1 x MRI scan (£334)	£828	NCL 400 Neurology Service WF01A/B Non-Admitted Face-to-Face Attendance, First / Follow-up[158] Pathology services, DAPS04 Clinical biochemistry, DAPS05 Haematology, DAPS09 Other[158] Multistix 10sg (£41.12 for 100)[161] Elective Inpatients DZ22K Unspecified Acute Lower Respiratory Infection with Interventions, with CC Score 9+[8] NCL Ophthalmology Service Non-Admitted Face-to-Face Attendance, First / Follow-up[158] RD07Z Magnetic Resonance Imaging Scan Requiring Extensive Patient Repositioning[158]
Natalizumab-IV or SC	1x neurology (NCL) first visit (£195.74) 1 x MRI scan (£334) 1x JC virus PCR (£247) [165] TA127[34] (£89.15)	£777	1x neurology (NCL) follow up visit (£184.23) 1 x MRI scan (£334) 1x JC virus PCR(£247)[165]	£765	NCL 400 Neurology Service WF01A/B Non-Admitted Face-to-Face Attendance, First / Follow-up[158] RD07Z Magnetic Resonance Imaging Scan Requiring Extensive Patient Repositioning[158]

Treatment	Year 1		Year 2 onwards		Source
	Resource Use	**Cost**	**Resource Use**	**Cost**	
Peginterferon -β-1a SC 125µg Interferon-beta-1a SC 44µg Interferon-beta-1a SC 22µg Interferon-beta-1a IM 30µg Interferon-beta-1b SC 250µg Glatiramer acetate SC 20 mg Glatiramer acetate SC 40 mg	1x neurology (NCL) first visit (£195.74) 4x neurology (NCL) follow up visits (£184.23) 5x liver function test (£3.35) 5x Full blood count (£3.37) 4x renal function test (£3.35) 1x Thyroid function test (£6.48) 1x MRI scan (£334)	£1,320	2x neurology (NCL) follow up visits (£184.23) 2x liver function test (£3.35) 2x renal function test ((£3.35) 1x MRI scan (£334)	£716	CIS Model assumptions[121] Non-Consultant Led (NCL) 400 Neurology Service WF01A/B Non-Admitted Face-to-Face Attendance, First / Follow-up[158] Pathology services, DAPS04 Clinical biochemistry, DAPS05 Haematology[158] Multistix 10sg (£41.12 for 100)[161] RD07Z Magnetic Resonance Imaging Scan Requiring Extensive Patient Repositioning[158]

Health state costs are from the multivariate regression analysis by Tyas et al[132] which combined the per-patient resource use from the 2005 UK MS survey by Orme et al[130] with per unit costs form other data sources to infer per-patient annual costs stratified by severity. These costs have been used extensively in TA767, TA699, TA533, TA312, TA254, T127, MTA (Teva submission). In TA533 it was noted 25% of direct non-medical costs are publicly funded and applicable to the NICE reference case. In TA312 the ERG preferred not to include direct non-medical costs from this analysis. The costs have been inflated to 2022/2023 prices using the NHSCII pay and prices index, details provided in Table 23.[157]

Table 23 Direct medical health state costs by severity, model formula A Tyas et al inflated to 2022/2023 prices

	2022/2023 prices	
	Estimate	**SE**
RRMS‡		
EDSS 0	£355	£2,807
EDSS 1	£121	£1,278
EDSS 2	£303	£1,234
EDSS 3	£1,208	£1,758
EDSS 4	£1,146	£1,257
EDSS 5	£2,017	£1,170
EDSS 6	£3,073	£1,210
EDSS 7	£9,358	£1,414
EDSS 8	£15,297	£1,520
EDSS 9	£21,494	£3,775
SPMS	£398	£1,002

‡ reference category

The costs of relapse were obtained from an analysis of the UK South West Impact of Multiple Sclerosis (SWIMS) project by Hawton and Green.[120] The study reported the proportions of patients treated for relapse or requiring hospitalisation and the 6 months costs associated. Annual costs were estimated and inflated to 2022/2023 prices.

Serious Adverse Events costs are assumed to be a single Natalizumab specific cost that was calculated as a weighted average of those reported in the AFFIRM trial.[77] The proportion of patients experiencing PML was provided by Biogen[154] using data from the 15 year final Analysis of the TOP study for the global population (n=6321) treated with Natalizumab.[155] Resource use for serious adverse events were based on previous technology appraisals[33, 34, 38] where available and updated to reflect the latest published reference costs.[158] These have been summarised in Table 24.

Table 24 Serious Adverse Events costs assumed for treatments in the model based on the AFFIRM trial

Serious Adverse Events	**Cost**	**Source**
Cholelithiasis	£9,006.35	GA10H Laparoscopic Cholecystectomy, 19 years and over, with CC Score 4+ (average on-elective long stay HRG cost)
Rehabilitation therapy	£618.38	VC12Z Rehabilitation for Other Neurological Disorders (average total HRG cost)
Urinary tract infection	£4,757.00	LA04H Kidney or Urinary Tract Infections, with Interventions, with CC Score 6-8 (average non-elective long stay HRG cost)

Serious Adverse Events	Cost	Source
Depression	£10,942.28	32x 713 WF01A-D Medical Psychotherapy Service total national average Non-Admitted Face-to-Face Attendance
Anaphylactic reaction	£910.96	313 Clinical immunology and allergy service Consultant led Multiprofessional Non-Admitted Non-Face-to-Face Attendance, First & Follow-up visits WH05Z Allergy or Adverse Allergic Reaction Day Case
Hypersensitivity reaction	£320.00	WH05Z Allergy or Adverse Allergic Reaction Day Case (average total HRG Cost)
Breast cancer	£14,212.82	CB0A1 Malignant, Ear, Nose, Mouth, Throat or Neck Disorders, with Interventions, with CC Score 9+ (average non-elective long stay HRG cost)
Gastritis	£706.54	FD05B Abdominal Pain without Interventions (average total HRG cost)
PML	£14,333.02	RD07Z Magnetic Resonance Imaging Scan Requiring Extensive Patient Repositioning (average total HRG cost £334) SA44A single Plasma Exchange (average non-elective long stay HRG cost £934) HC72A Diagnostic Spinal Puncture, 19 years and over (average non-elective inpatient long stay HRG cost £1,645.02) WH07A Hospitalisation Infections or other complications of procedures with Multiple Interventions with CC Score 2+ (average non-elective long stay HRG cost £11,420)

Patients who discontinue treatment are allowed to switch onto one of the higher line treatments. Patients who progress on to SPMS are assumed to be treated with Siponimod or beta-interferon for the remainder of their time in the model.

The standardized mortality ratio in base case analysis was reported in a case control study of (N=1822) MS patients follow-up up till death (Jick 2014).[139] An all-cause mortality Hazard ratio 1.68 (95% CI: 1.38-2.05) compared to the general population was estimated using a proportional hazards cox model.

6.5.5 Table of Model Inputs

A summary of all model input parameter, stochastic uncertainty and references are provided below in Table 25.

Table 25 Model inputs, stochastic distributions and sources of data.

Parameters	Estimate	Distribution	Source
Time Horizon	74 years (lifetime)	-	NICE reference case
Discounting	3.5%	-	NICE reference case
Population baseline characteristics			
Initial age	36	-	AFFIRM
Sex (female)	0.7	NA	AFFIRM
Initial EDSS Distribution	Table	Dirichlet	MS Registry in HA RRMS (Table)
Initial SPMS	0%	-	Decision problem is for patients without initial SPMS
Serious Adverse Events	Cholelithiasis§ (1%) Need for rehabilitation therapy § (1%)	NA	AFFIRM TOPS

Parameters	Estimate	Distribution	Source
‡ costs not modelled *§ disutility not modelled*	Urinary tract infection NOS (1%) Depression (1%) Anaphylactic reaction (1%) Hypersensitivity reaction (1%) Fall‡§ (1%) Breast cancer, NOS (1%) Convulsion, NOS‡§ (1%) Gastritis, NOS§ (1%) Cervical dysplasia‡§ (1%) Alcohol poisoning ‡§ (1%) Head injury‡§ (1%) Thermal burn‡§ (1%) PML (1%)		
Natural History			
Time to EDSS increase HARRMS Time to EDSS increase SPMS Time to EDSS decrease RRMS* Time to SP conversion HARRMS Time to relapse HARRMS Time to relapse SPMS	Estimates of parameters of the exponential survival models provided in results Section 6.8.1	Multivariate Normal on the log rate scale	MS Registry analysis
Baseline parameter			
Probability of SAEs	119 events on Natalizumab IV300 arm (n=627)	Beta	AFFIRM
Probability of discontinuation	38 events on Natalizumab IV300 arm (n=627)	Beta	AFFIRM
Proportion of relapses leading to hospitalisations	0.03500583	-	Hawton 2016[120]
Proportion treated with Siponimod	0.556962025	-	MS Registry
Mortality			
Life tables	General population mortality rates by age and sex	Piecewise exponential	ONS
Standard Mortality Ratio (SMR)	HR 1.68 (95%CI: 1.38-2.05) .	Normal on the Log HR	Jick et al[139]
SMR by EDSS	MR: 1.6 (Mild), 1.84(Moderate), 4.44 (severe).	Normal on the Log HR	Pokorski et al[166]
Treatment Effects			
CDP3	Log Hazard Ratios	Normal	NMA Section 5.1.3
CDP6	Log Hazard Ratios	Normal	NMA Section 5.1.3
ARR	Log Rate Ratios	Normal	NMA Section 5.1.2
SAEs	Log Hazard Ratios	Normal	NMA Section 5.1.5
Discontinuation	Log Hazard Ratios	Normal	NMA Section 5.1.5
Utilities			
Health State	Table 17	lognormal	Orme et al[130]
Carer	Table 18	lognormal	Acaster et al
Relapse	Table 17	Half normal	Orme et al
SAEs	Table 19	Half normal	See table for details
Costs			
Health State	Table 23	Gamma	Tyas et al

Parameters	Estimate	Distribution	Source
Treatment	Table 20	-	BNF
Administration	Table 21	Gamma	See table for details
Monitoring	Table 22	Gamma	See table for details
Relapse	relapse leading to hospialisation £8,638.21 (SD £4,168.25) Relapse treated with steroids £1,781.22 (SD £2,140.84)	Gamma	Hawton et al
SAEs	Table 24	Gamma	See table for details

* The MS Registry found no patients with highly active RRMS who decreased in EDSS so analysis could not be conducted. Model instead uses rate of EDSS decrease from all RRMS.

6.6 Analyses

The model and cost-effectiveness analysis were fully probabilistic with any specific parameter or structural sensitivity analyses also probabilistic.[126, 127]

6.6.1 Validation

A lack of validation and transparency for cost-effectiveness models can be significant barrier to their acceptance by stakeholders and decision makers in Health Technology Assessments (HTA).[167]

The International Society for Outcomes Research (ISPOR) and Society for Medical Decision Making (SMDM) taskforce on modelling have published significant guidelines on the need and methods for validation.[168] The taskforce identified five forms of validation: face validity, verification, cross validation, external validation, and predictive validation. Face validity of the RRMS model has been checked by clinical opinion and verification was checked by Javier Sanchez Alvarez at Evidera. Cross validation is conducted by comparing the estimates of one model with those of others, but this will not be conducted as requires full access to multiple RRMS models. External validation requires the comparison of model estimates with reports from independent external data. Given concerns about estimated occupancy of high EDSS states in TA767 and TA699 and the conversion to SPMS in TA699 and TA127, this is of importance to our RRMS model.[34, 41, 42] We therefore conducted an informal external validation of estimated EDSS against long-term data identified by the searches.

6.6.2 Cost-effectiveness analysis

Lifetime costs and QALYs were estimated. The mean over patient simulations was first calculated, removing individual variation and giving a lifetime cost and QALY estimate for each parameter sample. These were then summarised for each intervention/comparator using their mean and 95% CrI over parameter samples. Incremental costs and QALYs, summarised by means and 95% CrI, were calculated for each comparator compared to natalizumab and natalizumab biosimilar. Base case analyses used 1000 patients and 1000 samples while sensitivities used 100 patients and 100 samples. The number of patients to simulate and parameters to sample were tested by comparing the mean and 95% CrI, as calculated above, for 100, 250, 500, and 1000 patients and samples.

The primary analysis was a multiple treatment comparison under the net benefit framework. Net benefit and, relative to each intervention, incremental net benefit were calculated at willingness-to-pay of £20,000/QALY and £30,000/QALY. Their mean and 95%

CrI were calculated and the treatment with greatest net benefit interpreted as most cost-effective. Cost-effectiveness acceptability curves (CEAC).

A cost-effectiveness plane relative to natalizumab was included but not for natalizumab biosimilar; the high uncertainty and number of treatments give these planes little explanatory value.

A key sensitivity analysis excludes the cost for JCV testing on natalizumab, as a scheme is available whereby the manufacturer pays for this testing (Section 6.4). In this sensitivity, the cost is not excluded for the biosimilar as the scheme does not apply.

While the base case analysis used the cost of primary brands of comparators, a sensitivity analysis used the lowest price generic. This only modifies the price of glatiramer acetate (changing to Brabio manufactured by Viatris UK Healthcare Ltd) and fingolimod (changing to Fingolimod manufactured by Tillomed Laboratories Ltd).

Table 26 generic drug list prices

Drug	Mode	Qty.	Dose	Brand (Manufacturer)	Tariff Price	Indicative Price	delta
Glatiramer acetate	Injection	12	40 mg per 1 ml	Copaxone (Teva UK Ltd)	£513.95	£513.95	
Glatiramer acetate	Injection	12	40 mg per 1 ml	Brabio (Viatris UK Healthcare Ltd)	£513.95	£462.56	10.00%
Fingolimod	Capsule	28	0.5 mg	Gilenya (Novartis Pharmaceuticals UK Ltd)	£1,470.00	£1,470.00	
Fingolimod	Capsule	28	0.25 mg	Fingolimod (Novartis Pharmaceuticals Ltd)		£1,470.00	
Fingolimod	Capsule	28	0.5 mg	Fingolimod (Glenmark Pharmaceuticals Europe Ltd)	£1,470.00	£1,470.00	
Fingolimod	Capsule	28	0.5 mg	Fingolimod (Dr Reddy's Laboratories UK Ltd)	£1,470.00	£1,470.00	
Fingolimod	Capsule	28	0.5 mg	Fingolimod (Amarox UK Ltd)	£1,470.00	NA	
Fingolimod	Capsule	28	0.5 mg	Fingolimod (Sun Pharma UK Ltd)	£1,470.00	£1,470.00	
Fingolimod	Capsule	28	0.5 mg	Fingolimod (Accord UK Ltd)		£1,469.99	
Fingolimod	Capsule	28	0.5 mg	Fingolimod (Zentiva Pharma UK Ltd)	£1,470.00	£1,396.50	5.00%
Fingolimod	Capsule	28	0.5 mg	Fingolimod (A A H Pharmaceuticals Ltd)		£1,396.50	5.00%
Fingolimod	Capsule	28	0.5 mg	Fingolimod (Teva UK Ltd)	£1,470.00	£1,323.00	10.00%

Drug	Mode	Qty.	Dose	Brand (Manufacturer)	Tariff Price	Indicative Price	delta
Fingolimod	Capsule	28	0.5 mg	Fingolimod (Viatris UK Healthcare Ltd)	£1,470.00	£1,250.00	14.97%
Fingolimod	Capsule	28	0.5 mg	Fingolimod (Sandoz Ltd)	£1,470.00	£1,249.50	15.00%
Fingolimod	Capsule	28	0.5 mg	Fingolimod (Tillomed Laboratories Ltd)	£1,470.00	£367.50	75.00%

A summary of the base case and sensitivity cost-effectiveness analyses is provided in Table 27.

Table 27 Description of base case and sensitivity cost-effectiveness analyses

Analysis	Description
Base case	Uses HA RRMS from MS Registry for baseline rates on EDSS increase, progression to SPMS and time to relapse for HA RRMS patients. Uses all RRMS from MS Registry for EDSS decrease for HA RRMS patients. Uses all SPMS for EDSS increase and time to relapse for SPMS patients. All RRMS fixed effects from NMA for treatment effects, EDSS starting distribution from MS Registry for HA RRMS. Costs for primary bands are used for comparator drugs.
Scenario 1. Sensitivity using all RRMS and EDSS distribution for all RRMS from MS registry	Changes base case to better match the all RRMS population in the NMA. Uses all RRMS from the MS Registry for both baseline rates and the starting EDSS distribution for all RRMS
Scenario 2. Sensitivity using results of random effects NMAs	Changes base case to use the all RRMS random effects results from the NMA for treatment effects
Scenario 3. Sensitivity including JCV testing	Excludes the one-off cost of £247 associated with JCV testing for the natalizumab IV and SC interventions, but includes it for natalizumab biosimilar IV.
Scenario 4. Sensitivity using lowest price generic	Switches to using lowest price generic for comparators.
Scenario 5. Sensitivity assuming a reduction in Natalizumab-SC administration costs	Reduces administration cost by a factor of 0.5x for Natalizumab-SC to explore the company's assumption of reduced resource use (nurse administration hours per year). Increased capacity for service delivery at home(company funded) or in primary care setting.[34].
Scenario 6. Sensitivity using HA RRMS NMA	HARRMS on ARR only. all RRMS NMA for the other outcomes. Restricted to only the treatments which are included in the HA RRMS NMA for ARR (i.e., alemtuzumab, cladribine, fingolimod, interferon beta 1a, natalizumab IV, ocrelizumab IV)
Scenario 7. Sensitivity using mortality rates stratified by disease severity	Mortality ratios calculated using a Chi square table for MS patients stratified by mild (n=1394), moderate (n=789) and severe (n=165) in analysis by the MS Society of Canada between 1972-1985, by Sadovnik et al 1992 and cited in Pokorski et al 1997. These ratios are widely used in MS appraisals; TA767, TA699, TA533, TA312, TA254 TA127.
Scenario 8. Sensitivity assuming clinical equivalence for natalizumab and natalizumab biosimilar	Assumes all treatment effects on efficacy and safety outcomes for natalizumab biosimilar IV to be the same as natalizumab IV
Scenario 9. Sensitivity using EID for natalizumab and natalizumab biosimilar	Uses extended interval dosing (EID) for natalizumab IV, natalizumab SC, and natalizumab biosimilar IV
Scenario 10. Sensitivity using OPERA utilities for RRMS	Uses the RRMS utilities from OPERA described in Table 17 for RRMS

Analysis	Description
Scenario 11. Sensitivity using CLARITY utilities for RRMS	Uses the RRMS utilities from CLARITY described in Table 17 for RRMS
Scenario 12. Sensitivity using TA127 for carer disutilities	Uses the TA127 carer disutilities described in Table 18
Scenario 13. Sensitivity using EDSS specific mortality	Uses EDSS specific mortality data from Harding et al[169] (for EDSS≥4 and base case SMR for EDSS<4) as preferred by committee in the recent cladribine appraisal (ID6263).[170]
Scenario 14. Using NMA where CDP3 is used for studies with missing CDP6	Uses the NMA estimates from Table 76.
Scenario 14. Sensitivity using lowest regional prices for alemtuzumab and cladribine (cPAS appendix only)	Uses lowest regional price for alemtuzumab and cladribine
Scenario 15. Sensitivity using highest regional prices for alemtuzumab and cladribine (cPAS appendix only)	Uses highest regional price for alemtuzumab and cladribine

Table 28 Assumptions of the cost-effectiveness base case analysis*

Cohort assumed to start at age 36, be 70% female
All patients assumed to start in HA RRMS (not SPMS) with EDSS distribution from MS Registry HA RRMS patients (Table)
Baseline rates of EDSS increase and relapse estimated by exponential model applied to natalizumab HA RRMS patients of MS Registry
Treatment effects on EDSS increase informed by all RRMS fixed effects NMA on CDP6
Treatment effects on relapse rate informed by all RRMS fixed effects NMA on ARR
Efficacy and safety treatment effects for natalizumab and natalizumab biosimilar assumed different and informed by NMA
Treatments missing from NMA were assumed to be equivalent to treatments with the same class; Ponesimod and Fingolimod, Interferon-beta-1a SC 44µg and Interferon-beta-1a SC 22µg, Ofatumumab and Ocrelizumab, Glatiramer acetate SC 20 mg and Glatiramer acetate SC 40 mg.
Rates of EDSS decrease estimated by exponential model applied to all RRMS patients of MS Registry (no HA RRMS patients experienced decrease in EDSS so could not be estimated in HA RRMS population).
Rates of progression to SPMS estimated by exponential model applied to HA RRMS patients of MS Registry
Rates of EDSS increase and relapse in SPMS estimated by exponential model applied to SPMS patients of MS Registry.
SPMS patients assumed not to experience EDSS decrease
No effect assumed by RRMS treatment on event rates after progression to SPMS
EDSS starting distribution from MS Registry for HA RRMS.
Baseline treatment discontinuation rate informed by discontinuation due to AE on natalizumab arm of AFFIRM
Treatment effects on discontinuation informed by all RRMS fixed effects NMA on discontinuation due to AE
Patients stop treatment after reaching EDSS 7.0 (with “no treatment” modelled as placebo effect from NMA)
Baseline serious AE rate informed by natalizumab arm of AFFIRM
Treatment effects on serious adverse event rate informed by all RRMS fixed effects NMA on serious AEs
General population mortality stratified by age and sex and informed by ONS life tables
SMR of 1.68 (95% CI: 1.38-2.05) not assumed to vary by EDSS and informed by 1822 MS patients in Jick 2014.[139]
Costs for primary bands are used for comparator drugs.
Includes the one-off cost of £247 associated with JCV testing for natalizumab IV, natalizumab SC, and natalizumab IV biosimilar
List prices from BNF used for all treatments, with price of named brands used for comparators where appropriate

Natalizumab IV and SC assumed to have the same administration costs
RRMS utilities stratified by EDSS and RRMS utility follows results of UK MS Survey 2005 Orme et al (Table 17).[130]
Carer disutilities stratified by EDSS and informed survey of 200 caregivers by Acaster et al (Table 18).[171]
Relapse disutilities informed by Orme et al (Table 17).[130]
SAEs in the model were urinary tract infection, depression, anaphylactic reaction, hypersensitivity reaction, breast cancer, gastritis and PML
Disutilities for SAEs followed those reported in previous RRMS appraisals (Table 19)
Annual costs for RRMS patients stratified by EDSS severity and for SPMS patients follow per-patient resource use costs from 2005 UK MS Survey (Tyas et al) and unit costs from Orme et al.[130, 132]
Administration costs for years 1 and 2 in Table 21, and those for monitoring costs for years 1 and 2 in Table 22
Relapse costs from Hawton et al (Table 23)
SAE costs follow sources described in Table 24

*Input parameters not specified are provided in Table 25 and linked tables.

6.6.3 Value of information analysis

Parameter uncertainty was quantified using value of information analysis.[172] The per-person expected value of partial perfect information (EVPPI) was estimated for each parameter or for groups of parameters of interest (e.g., each efficacy and safety treatment effect from the NMA, baseline rates from the MS Registry, utilities, uncertain costs, discontinuation rates, and SAE rates). These constitute a large number of uncertain parameters as, for example, there are 10+ treatments on which we would have treatment effects. We therefore use the Bayesian additive regression trees (BART) method, as implemented in the R package VOI, for EVPPI estimation due to its suitability for EVPPI of many parameters. Alternatives we considered were Generalised additive models (GAM), Gaussian processes (GP), and, if found necessary, Multilevel Monte Carlo (MLMC) simulation were used to estimate EVPPI.[173, 174] This per-person EVPPI was used as the probabilistic decision-theoretic alternative to one-way deterministic sensitivity analysis.

If evidence were available on the incidence of 2nd line highly active RRMS, the population EVPPI could be estimated. However, no evidence on this incidence was identified so only per person EVPPI was included.

6.6.4 Software

The model will be coded in the R programming language.[63, 175, 176] The 'DESCEM package was used for the implementation of DES, 'BCEA' will be used for generating the CEACs and CEAFs, and both 'BCEA' and 'VOI' will be used for value of information analysis.[176] This work will be carried out using the computational facilities of the Advanced Computing Research Centre, University of Bristol - http://www.bristol.ac.uk/acrc/.

6.7 Changes from the protocol

The model was changed so that there would be no treatment effects on SPMS progression or mortality. The SLR found no data on SPMS progression. Mortality was not included by the SLR as an outcome of interest, but it was not widely reported. MS may reduce life expectancy, with a recent study estimating life expectancy to be 75.9 years in an MS population compared to 83.4 years in a population matched on sex, age, and region. [9] However, the studies generally included patients in their 30s and 40s so would not be expected to find a great impact on mortality.

The software for model implementation was unchanged but the 'DESCEM' package was used instead of 'simmer' due to its greater focus on health economic modelling.

The targeted search for placebo and standard of care outcomes, and the review of health related quality of life, were not undertaken.

The targeted search on placebo and standard of care outcomes was replaced by an analysis of individual patient data from the UK MS Registry (Section 6.5.2).

The "desirable quested analyses" from the MS Registry were removed as were not conducted. These were to estimated EQ-5D-5L for RRMS and SPMS and to model treatment switching patterns.

We removed the plan to calculate ICERs so as to focus interpretation on the total and incremental net benefits. We kept only one cost-effectiveness plane (for natalizumab-IV) as the uncertainty gave it little explanatory power. We included the CEAC but because of the number of treatments, and that non-natalizumab treatments were coming out with highest probabilities, we decided against including the cost-effectiveness acceptability frontiers.

Only per person EVPPI is calculated as we did not find an estimate of the incidence of HA RRMS that corresponded to our definition.

The ratio of EVPPI to EVPI was not calculated as the number of uncertain parameters in the economic model was 247. We instead calculated the EVPPI of substantial groups of parameters.

Validation was limited to a comparison of EDSS severity over time and not SPMS status, as only evidence on EDSS severity could be found by the literature searches.

6.8 Model Results

6.8.1 Results of the MS Registry analyses

The results of the MS registry analyses exponential survival models are summarised in Table 30 (treatment dependent rates) and Table 32 (treatment independent rates). Samples sizes for the treatment dependent models are in Table 31, while those treatment independent models are in Table 32. These coefficients are on the log scale and the total log rate is calculated by adding the relevant components (i.e., the intercept plus the product of the current EDSS category with EDSS coefficient in all models, plus the coefficient for natalizumab in the treatment dependent models). The covariance matrices for the coefficients are provided in Appendix 7. The economic model was probabilistic so coefficients are sampled from multivariate normal with means in Table 30 and Table 32 and covariance matrices in Appendix 7. The MS Registry found no patients with highly active RRMS who decreased in EDSS so analysis could not be conducted.

Table 29 Number of Highly Active RRMS and RRMS patients by severity state in the MS Registry data set.*

EDSS	0	1	2	3	4	5	6	7	8	9
HARRMS	29	6	56	36	56	26	82	10	0	0
RRMS	50	18	200	188	150	90	214	45	5	0

*301 patients in total in HARRMS and 960 in RRMS.

The results of the multistate model are provided in Appendix 7. Due to the low sample size for the transitions between 9 different EDSS states, the log rates were very extreme between low severity states. For example, the mean rate (i.e., exponent of the log rates) between from EDSS 1 to EDSS 0 was 1041.7, EDSS 0 to EDSS 1 was 434.6 and from EDSS 2 to EDSS 3 was 83.0. It was decided to use only the exponential survival models for EDSS increase and decrease events in the economic model.

Table 30 Log rates and log rate ratios for events with treatment dependence estimated by the MS Registry using exponential survival models*

	Times to EDSS Increase (RRMS Highly Active)	Times to EDSS Increase (All RRMS)	Time to Relapse (RRMS Highly Active)	Time to Relapse (All RMS)
Intercept	-0.93 (-1.94, 0.07)	-2.25 (-2.63, -1.86)	-2.13 (-2.95, -1.3)	-2.63 (-3.08, -2.18)
EDSS	-0.18 (-0.33, -0.03)	-0.17 (-0.25, -0.1)	-0.02 (-0.2, 0.17)	-0.07 (-0.16, 0.01)
Alemtuzumab	-0.34 (-1.49, 0.81)	0.05 (-0.68, 0.78)	0.02 (-2.07, 2.12)	0.18 (-0.58, 0.93)
Cladribine	-3.29 (-5.44, -1.14)	-1.17 (-2.35, 0)	-0.79 (-2.87, 1.29)	0.37 (-1.05, 1.79)
Fingolimod	-2.38 (-3.53, -1.23)	-0.53 (-1.05, -0.01)	-0.21 (-1.1, 0.68)	0.13 (-0.34, 0.6)
Glatiramer Acetate	-1.04 (-2.23, 0.16)	-0.3 (-0.81, 0.2)	-0.52 (-1.49, 0.45)	0.04 (-0.39, 0.48)
Natalizumab	-1.26 (-2.5, -0.02)	0.28 (-0.17, 0.72)	-0.74 (-1.92, 0.43)	0.4 (-0.1, 0.9)
Ocrelizumab	-1.05 (-2.09, 0)	0.37 (-0.06, 0.8)	-0.17 (-1.4, 1.05)	0.29 (-0.36, 0.93)
Ofatumumab	-1.81 (-3.24, -0.38)	-0.02 (-0.72, 0.67)	-1.03 (-3.11, 1.05)	-0.1 (-1.53, 1.32)
Ponesimod	-1.43 (-3.58, 0.72)	-0.51 (-2.49, 1.48)	-0.38 (-2.46, 1.7)	0.23 (-1.76, 2.22)

*The economic model only used the intercept, effect of EDSS, and effect of natalizumab.

Table 31 Samples sizes in MS Registry analyses for treatment dependent events*

Event	N	Alemtuzumab	Cladribine	Fingolimod	Glatiramer acetate	Natalizumab	Ocrelizumab	Ofatumumab	Ponesimod
Time to EDSS Increase (RRMS Highly Active)	224	12	23	65	20	23	43	25	4
Time to EDSS Increase (All RRMS)	1016	41	35	158	158	177	203	69	7
Time to Relapse (RRMS Highly Active)	50	1	1	13	11	7	4	1	1
Time to Relapse (All RRMS)	191	9	2	34	44	28	15	2	1

* The MS Registry found no patients with highly active RRMS who decreased in EDSS so analysis could not be conducted.

Table 32 Log rates and log rate ratios for events with no treatment dependence estimated by the MS Registry using exponential survival models

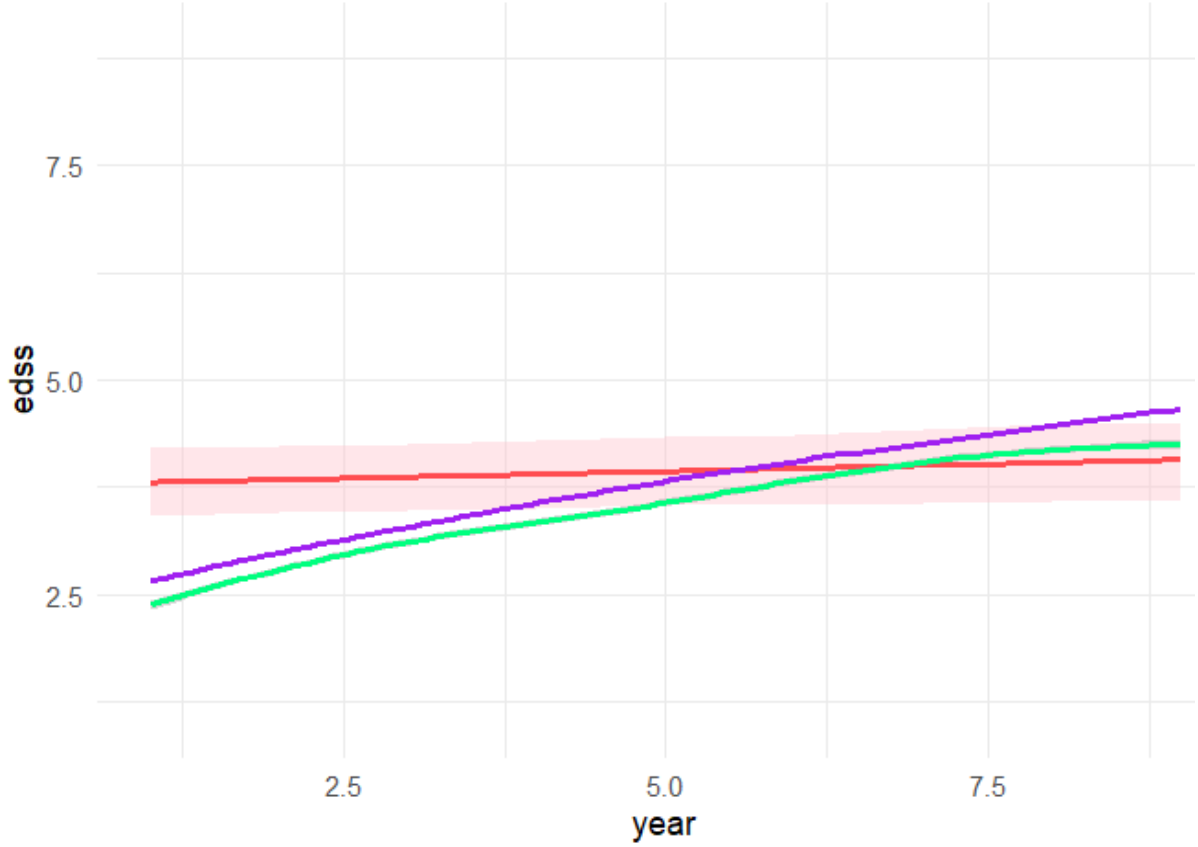
	Time to EDSS Decrease (All RRMS)*	Time to EDSS Increase (SPMS)	Time to Relapse (SPMS)	Time to SPMS Conversion (RRMS Highly Active)	Time to SPMS Conversion (All RRMS)
Sample size	793	181	164	66	222
Rate	-3.51 (-3.94, -3.08)	-1.89 (-3.15, -0.63)	-4.83 (-6.66, -3.01)	-2.58 (-3.89, -1.26)	-2.81 (-3.52, -2.1)
EDSS	0.14 (0.04, 0.23)	-0.2 (-0.42, 0.01)	0.07 (-0.22, 0.36)	0.01 (-0.21, 0.23)	0.04 (-0.08, 0.15)

* The MS Registry found no patients with highly active RRMS who decreased in EDSS so analysis could not be conducted.

6.8.2 Validation

The model code was validated by Javier Sanchez Alvarez at Evidera who found no major issues but suggested some minor improvements to flow and usage of DESCEM.

Figure 25 Validation through comparison of EDSS severity over time from economic model (red line with 95% CrI) and predictions from Palace 2014 (purple and green)



We compare the model's predictions to a continuous-time Markov model fit in to predict EDSS progression in a natural history cohort based on entry demographic and clinical data, but which did not distinguish between RRMS and SPMS, was not specific to highly active RRMS, and only included treatment with beta interferons rather than the latest DMT sequences. The model was fit in a cohort of the UK Risk Sharing Scheme and validated in a closely matched cohort from the British Columbia Canada Data set.[177] The mean (redline)

and 95% CrI (shaded area) severity over the first 10 years in our DES model. The purple and green lines are the predicted and observed mean severity over the same time period in the published continuous-time Markov models.[128] The general overlap over this 10 year period is poor and the progression of the DES is less marked. This is likely explained by the comparator model being developed for both RRMS and SPMS and not including the latest DMT sequences.

6.8.3 Base case analysis

The results of the convergence test are in Table 33. This shows that the mean and 95% CrI for total costs, QALYs, and net benefits for natalizumab-IV are somewhat stable with only 100 patients and 100 samples. The QALYs are potentially unstable below 500 samples and 250 patients but not to the extent that could affect results. We can therefore use 100 patients and 100 samples for sensitivity analysis as this is sufficient to demonstrate sensitivity or otherwise to the explored assumption.

Table 33 Assessment of convergence of economic model using mean and 95% CrI for natalizumab-IV (publicly available list prices)

		100 samples	250 samples	500 samples	1000 samples
Total costs	**100 patients**	338085.31 (281287.49, 391866.81)	337470.91 (284171.66, 391919.16)	338330.84 (287442.85, 391895.71)	338478.09 (287390.59, 397941.21)
	250 patients	337581.60 (285952.72, 385790.24)	336997.32 (284070.61, 386941.95)	338408.45 (288630.84, 394100.87)	338331.21 (289346.69, 396083.60)
	500 patients	337958.51 (289387.89, 385856.00)	336879.21 (284163.83, 386871.07)	338155.13 (289369.44, 394721.12)	338212.38 (288732.68, 395581.66)
	1000 patients	337528.08 (289132.13, 388675.87)	336616.92 (287468.64, 389082.47)	337984.58 (289378.10, 393917.33)	338200.53 (288303.59, 397676.67)
Total QALYs	**100 patients**	9.026 (6.325, 11.715)	9.019 (6.565, 11.367)	9.075 (6.618, 11.324)	9.079 (6.463, 11.488)
	250 patients	9.033 (6.463, 11.547)	9.023 (6.641, 11.158)	9.091 (6.682, 11.163)	9.101 (6.580, 11.302)
	500 patients	9.040 (6.446, 11.453)	9.011 (6.694, 11.171)	9.084 (6.672, 11.255)	9.092 (6.574, 11.333)
	1000 patients	9.062 (6.389, 11.358)	9.033 (6.610, 11.220)	9.093 (6.628, 11.333)	9.095 (6.609, 11.360)
Net benefit at £20,000/QALY	**100 patients**	-157572.27 (-215261.01, -98587.46)	-157097.29 (-214717.85, -101660.54)	-156820.96 (-214919.87, -101061.21)	-156907.34 (-216509.46, -102440.98)
	250 patients	-156929.78 (-209220.08, -104908.31)	-156540.68 (-203074.96, -109325.38)	-156595.75 (-210204.05, -106941.36)	-156305.32 (-212010.45, -106267.56)
	500 patients	-157165.16 (-207819.87, -107640.44)	-156654.52 (-206110.60, -109913.05)	-156477.55 (-210664.83, -105733.62)	-156375.04 (-211927.21, -105359.14)
	1000 patients	-156293.56 (-208708.30, -108728.77)	-155957.71 (-206200.82, -112836.17)	-156120.77 (-208771.97, -106106.05)	-156305.50 (-212533.02, -105769.56)

		100 samples	250 samples	500 samples	1000 samples
Net benefit at £30,000/QALY	**100 patients**	-67315.75 (-145700.14, 7054.88)	-66910.48 (-138839.10, 4003.79)	-66066.01 (-137315.75, 2689.65)	-66121.97 (-137807.04, 2543.69)
	250 patients	-66603.87 (-136780.94, 112.11)	-66312.36 (-128886.38, -5969.55)	-65689.41 (-131465.95, -2796.44)	-65292.37 (-132551.22, -2150.00)
	500 patients	-66768.49 (-142208.82, -3936.29)	-66542.18 (-130346.10, -7805.63)	-65638.76 (-131815.71, -5001.83)	-65456.37 (-133428.85, -4398.92)
	1000 patients	-65676.30 (-141977.42, -6865.16)	-65628.11 (-130975.14, -7964.30)	-65188.87 (-131648.68, -5093.74)	-65357.99 (-136494.89, -4390.50)

The results of the base case analysis using the HARRMS population from the MS Registry and base case NMA results (i.e., fixed effects analysis in the All RRMS population) are provided in this section. We used 1000 samples and 1000 patients for this simulation. Uncertainty, as indicated by the 95% CrI is very high but general patterns can be seen.

With the exception of ocrelizumab, all treatments had greater net benefit at £20-30,000/QALY than natalizumab-IV, natalizumab biosimilar-IV and natalizumab-SC. The 95% CrI for incremental net benefits relative to natalizumab-IV excluded zero and the 95% CrI for net benefits for natalizumab biosimilar-IV and natalizumab-SC were not overlapping with those of comparators, indicating confidence that the net benefits of the natalizumabs are lower. Ocrelizumab had lower net benefit than any of the natalizumabs. Natalizumab-IV has lower net benefit at £20-30,000/QALY than natalizumab biosimilar-IV, although the 95% CrI overlap with 0.0 indicating no evidence of a difference in net benefits. Natalizumab-SC has very similar mean net benefit to Natalizumab-IV.

Across treatments, interferon-beta-1b SC 250µg has the greatest net monetary benefit at £20-30,000/QALY, followed by glatiramer Acetate 20mg, glatiramer acetate 40mg, interferon-beta-1a SC 44µg, and peginterferon -β-1 SC 125µg.

Table 34 Net Benefit and incremental net benefit in for treatments in comparison to Natalizumab IV (Public list prices) for the base case (HARRMS)

Treatment	Net benefit at £20,000/QALY (95% CrI)	Net benefit at £30,000/QALY (95% CrI)	INB at £20,000/QALY (95% CrI)	INB at £30,000/QALY (95% CrI)	CEAC at £20,000/QALY	CEAC at £30,000/QALY
Natalizumab -IV	-156305.50 (-212533.02, -105769.56)	-65357.99 (-136494.89, -4390.50)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0	0
Natalizumab -SC	-156808.14 (-214094.00,	-65880.08 (-134504.65, -1099.19)	-502.64 (-16551.93, 16092.39)	-522.09 (-17946.95, 16796.23)	0	0

Treatment	Net benefit at £20,000/QALY (95% CrI)	Net benefit at £30,000/QALY (95% CrI)	INB at £20,000/QALY (95% CrI)	INB at £30,000/QALY (95% CrI)	CEAC at £20,000/QALY	CEAC at £30,000/QALY
	-106946.45)					
Natalizumab biosimilar-IV	-147098.62 (-203963.94, -100597.27)	-56213.75 (-124896.35, 4969.52)	9206.89 (-7313.60, 27383.20)	9144.24 (-8856.05, 28394.97)	0	0
Fingolimod	-136976.72 (-189337.78, -94058.23)	-47009.62 (-111475.58, 12515.07)	19328.78 (1875.72, 42263.48)	18348.37 (-1154.99, 42675.66)	0	0
Alemtuzumab	-102904.10 (-169817.14, -46296.15)	-11437.45 (-99328.09, 62322.08)	53401.40 (-7103.10, 126307.28)	53920.54 (-8390.93, 128553.65)	0	0
Cladribine	-86716.48 (-152472.55, -26832.12)	1650.49 (-91245.97, 80628.42)	69589.03 (12588.27, 140227.70)	67008.48 (9544.84, 140804.95)	0	0
Ponesimod	-99334.18 (-158490.80, -57356.83)	-9949.03 (-90111.86, 50559.41)	56971.32 (27400.25, 92534.88)	55408.96 (23033.04, 92103.02)	0	0
Ofatumumab	-146159.89 (-198425.25, -99847.27)	-55077.49 (-123093.90, 5829.32)	10145.61 (-5193.92, 25898.05)	10280.50 (-8162.22, 28179.71)	0	0
Ocrelizumab	-157786.52 (-212564.67, -107265.27)	-66537.84 (-135055.61, -2359.17)	-1481.02 (-16697.29, 12669.42)	-1179.85 (-19531.68, 15710.44)	0	0
Peginterferon -β-1 SC 125µg	-52408.08 (-112753.52, -3961.83)	38310.49 (-42698.13, 103548.02)	103897.42 (53635.73, 162561.20)	103668.48 (51467.09, 161755.27)	0.015	0.027
Interferon-beta-1a SC 22µg	-64633.03 (-129779.60, -16275.41)	24703.61 (-64008.59, 92278.54)	91672.47 (43468.36, 146183.52)	90061.60 (38607.49, 147656.29)	0	0
Interferon-beta-1a SC 44µg	-52235.14 (-113722.53, -1707.82)	37379.38 (-45453.50, 107768.09)	104070.37 (52949.57, 164025.84)	102737.37 (49237.91, 163673.72)	0.028	0.042
Interferon-beta-1a IM 30µg	-55518.90 (-	33982.89 (-57882.08, 104303.96)	100786.61 (50753.11, 158377.71)	99340.88 (47499.75, 159353.18)	0.004	0.011

Treatment	Net benefit at £20,000/QALY (95% CrI)	Net benefit at £30,000/QALY (95% CrI)	INB at £20,000/QALY (95% CrI)	INB at £30,000/QALY (95% CrI)	CEAC at £20,000/QALY	CEAC at £30,000/QALY
	118867.17, -5335.40)					
Interferon-beta-1b SC 250µg	-43678.07 (-102879.85, 5822.55)	48214.07 (-33902.25, 116098.83)	112627.43 (59720.87, 171813.41)	113572.06 (58682.25, 174340.67)	0.441	0.483
Glatiramer Acetate 20mg	-46073.49 (-114260.07, 3601.09)	43518.35 (-48828.65, 113825.10)	110232.01 (56926.28, 171622.40)	108876.34 (54279.66, 170529.85)	0.256	0.213
Glatiramer Acetate 40mg	-46135.27 (-111505.17, 5443.03)	43483.22 (-49299.92, 113381.07)	110170.24 (55732.39, 173179.13)	108841.21 (52428.23, 175299.49)	0.256	0.224

The total costs and QALYs for all included treatments, and their incremental comparison with Natalizumab IV, are provided in Table 35. The 95% CrI for both costs and QALYs are wide, suggesting high uncertainty. All treatments, with the exception of ocrelizumab have lower costs than natalizumab-IV with 95% CrI for incremental costs excluding 0.0 and indicating that costs are lower on the comparators. Except for ocrelizumab, and ofatumumab in comparison with natalizumab biosimilar-IV, all 95% CrI for costs on comparators do not overlap with those for natalizumab biosimilar-IV or natalizumab SC, suggesting costs are also higher. The 95% CrI for QALYs were overlapping suggesting no difference, although the mean QALYs were lower on most treatments than on the natalizumab. The exceptions were alemtuzumab, ofatumumab, and ocrelizumab, which had higher mean QALYs (although ofatumumab was tied with natalizumab-SC).

The natalizumab biosimilar-IV has lower costs but also lower QALYs than natalizumab-IV. However the differences in costs and QALYs are uncertain with 95% CrI overlapping. The 95% CrI for incremental costs and QALYs of natalizumab biosimilar-IV and natalizumab-IV are overlapping with 0.0 suggesting no evidence of a difference in costs or QALYs. Natalizumab-SC has very similar costs and QALYs to natalizumab-IV.

Across treatments, total costs are lower on fingolimod, alemtuzumab, cladribine, ponesimod, Peginterferon -β-1 SC 125µg, interferon-beta-1a SC 22µg, interferon-beta-1a SC 44µg, interferon-beta-1a IM 30µg, interferon-beta-1b SC 250µg, glatiramer Acetate 20mg, and glatiramer Acetate 40mg than on the natalizumab-IV with 95% CrI that do not overlap. QALYs appear to be lower on all treatments, with the exception of alemtuzumab, ofatumumab, ocrelizumab, and interferon-beta-1b SC 250µg, but uncertainty is higher and the 95% CrI are overlapping.

We see that interferon-beta-1b SC 250µg and alemtuzumab have greatest mean QALYs, followed by ocrelizumab. The higher QALYs for interferon-beta-1b SC 250µg are driven by its having the lowest rate of CDP6 (i.e., EDSS increase), as informed by the NMA (Figure 6).

Ocrelizumab also has the highest costs, followed by natalizumab-SC, which is almost level with natalizumab-IV. The favourable net benefits for glatiramer Acetate 20mg, glatiramer acetate 40mg, and interferon-beta-1a SC 44µg, and peginterferon-β-1 SC 125µg, are seen to be driven by their having the lowest costs, despite their low QALYs.

ICERs comparing the natalizumab-IV to each of the other treatments are provided for completeness, but decision making should focus on the incremental net benefits as they better capture the high degree of uncertainty in this analysis. We see that only natalizumab-SC is dominated by natalizumab-IV while alemtuzumab, ofatumumab and interferon-beta-1b SC 250µg dominate natalizumab-IV. Compared to ocrelizumab, natalizumab-IV is in the South-West quadrant, with lower costs and higher QALYs. In all other cases the ICER is above £20-30,000/QALY, suggesting it is not cost-effective.

Undiscounted total costs and QALYs are also provided in Table 36.

Table 35 Total and incremental costs and QALYs and ICERs for Natalizumab IV in comparison to treatments (Public list prices) for the base case (HARRMS)

Treatment	Total costs £	Total QALYs	Incremental costs £	Incremental QALYs	ICER (£/QALY)*
Natalizumab-IV	338,200.53	9.094751	0.00	0	0.00
Natalizumab-SC	338,664.27	9.092806	-463.74	0.001945	Dominant
Natalizumab biosimilar-IV	328,868.34	9.088486	9,332.19	0.006265	1,489,517.06
Fingolimod	316,910.92	8.99671	21,289.61	0.098042	217,148.71
Alemtuzumab	285,837.41	9.146665	52,363.13	-0.05191	Dominated
Cladribine	263,450.41	8.836696	74,750.13	0.258055	289,667.38
Ponesimod	278,104.50	8.938516	60,096.03	0.156236	384,650.15
Ofatumumab	328,324.69	9.10824	9,875.84	-0.01349	Dominated
Ocrelizumab	340,283.88	9.124868	-2,083.35	-0.03012	69,176.36‡
Peginterferon -β-1 SC 125µg	233,845.22	9.071857	104,355.31	0.022895	4,558,071.67
Interferon-beta-1a SC 22µg	243,306.32	8.933664	94,894.21	0.161087	589,086.62
Interferon-beta-1a SC 44µg	231,464.16	8.961451	106,736.37	0.1333	800,721.95
Interferon-beta-1a IM 30µg	234,522.47	8.950178	103,678.07	0.144573	717,132.85
Interferon-beta-1b SC 250µg	227,462.36	9.189214	110,738.18	-0.09446	Dominated
Glatiramer Acetate 20mg	225,257.19	8.959185	112,943.35	0.135567	833,119.67
Glatiramer Acetate 40mg	225,372.24	8.961848	112,828.30	0.132903	848,951.86

‡located in South West (SW) quadrant of cost-effectiveness plane. *Not reported if natalizumab-IV is Dominant or Dominated

Table 36 Total undiscounted costs and QALYs for treatments (Public list prices) for the base case (HARRMS)

Treatment	Total undiscounted costs £ (95% CrI)	Total undiscounted QALYs (95% CrI)
Natalizumab-IV	583542.87 (489210.53, 705568.01)	16.88 (11.41, 22.04)
Natalizumab-SC	581659.01 (491086.45, 718636.40)	16.95 (12.10, 22.58)
Natalizumab biosimilar-IV	572185.37 (481463.15, 675184.24)	16.89 (12.25, 22.80)
Fingolimod	573023.41 (478761.99, 714119.86)	16.96 (12.13, 22.15)
Alemtuzumab	552978.44 (475343.61, 676646.67)	16.64 (12.13, 22.04)
Cladribine	489596.53 (414614.03, 586524.05)	17.19 (11.62, 22.49)
Ponesimod	471320.05 (409048.10, 580031.43)	16.45 (11.19, 22.04)
Ofatumumab	506491.18 (437993.40, 589535.25)	16.66 (11.71, 22.02)
Ocrelizumab	569823.03 (484256.03, 694239.91)	16.93 (12.13, 22.94)
Peginterferon -β-1 SC 125µg	594150.02 (491882.32, 729377.54)	17.12 (13.40, 22.20)
Interferon-beta-1a SC 22µg	448157.84 (398072.43, 534519.33)	16.77 (12.15, 22.07)
Interferon-beta-1a SC 44µg	460627.65 (403143.91, 535452.29)	16.70 (11.46, 22.75)
Interferon-beta-1a IM 30µg	444085.98 (396991.69, 521670.91)	16.69 (11.50, 21.85)
Interferon-beta-1b SC 250µg	446689.26 (394328.34, 532965.39)	16.52 (10.24, 21.83)
Glatiramer Acetate 20mg	438526.85 (382254.89, 529307.80)	17.41 (12.68, 22.47)
Glatiramer Acetate 40mg	440079.68 (378110.08, 523976.18)	16.61 (11.18, 22.13)

The cost-effectiveness plane and CEAC are presented in Figure 26 and Figure 27, respectively. The cost-effectiveness plane graphically illustrates the high uncertainty in incremental costs and effects of Table 35. It also makes it clear that natalizumab-IV is very unlikely to be cost-effective at a £30,000/QALY willingness-to-pay threshold compared to any of the treatments. The CEAC confirms the finding that glatiramer Acetate 20mg, glatiramer acetate 40mg, and interferon-beta-1b SC 250µg are most likely to be cost-effective in the £20-30,000/QALY range. These CEAC values at £20,000/QALY and £30,000/QALY are also reported in Table 34. The probability that interferon-beta-1b SC

250µg is only approximately 50%, indicating uncertainty as to which is most cost-effective. The natalizumabs have close to 0% chance of having highest net benefit (CEAC) at £20,000/QALY and £30,000/QALY.

Figure 26 Cost-Effectiveness Plane for treatments in comparison to Natalizumab IV, WTP £30,000/QALY (Public list prices) for the base case (HARRMS)

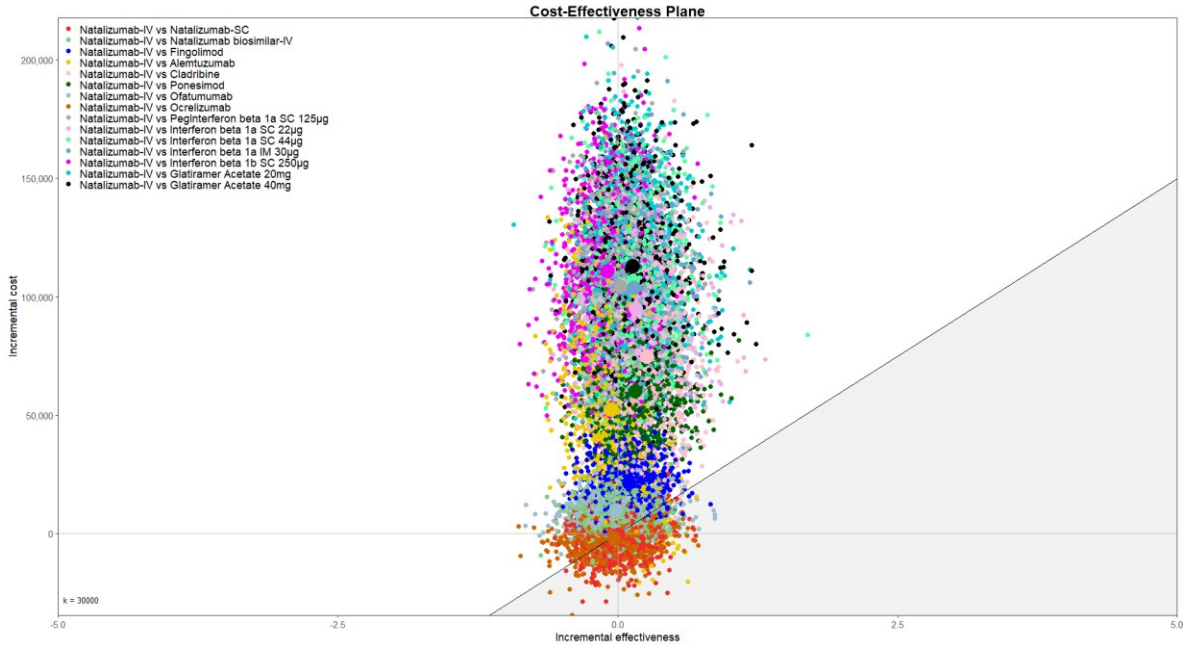
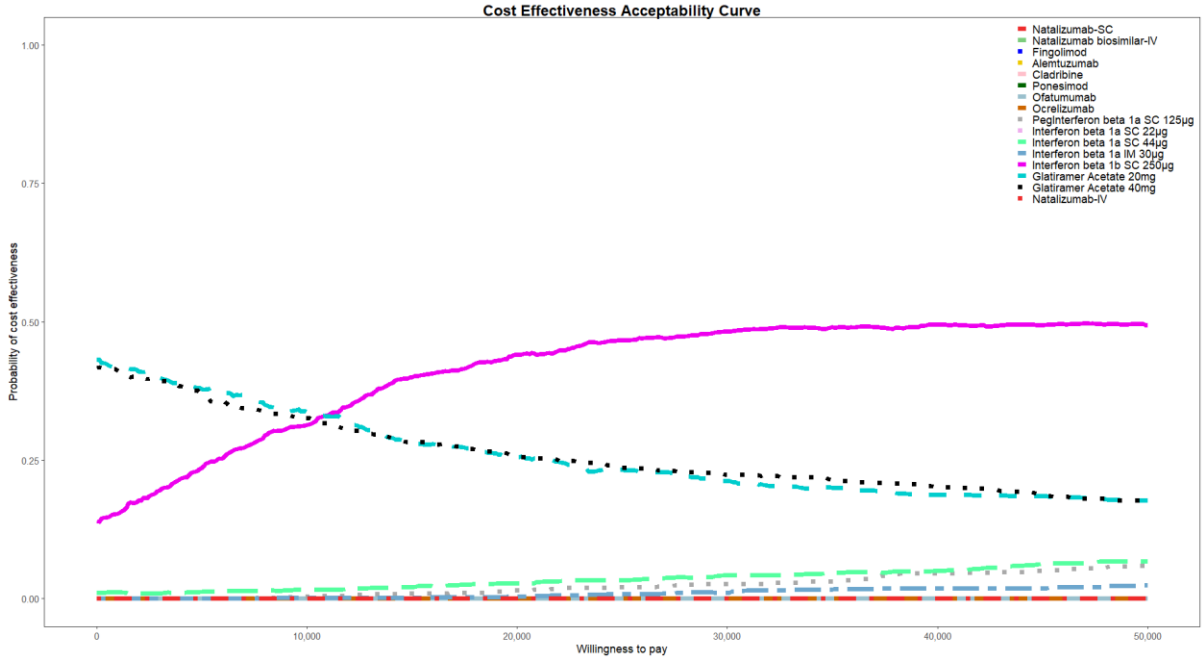


Figure 27 Cost Effectiveness Acceptability Curve for treatments in comparison to Natalizumab IV, WTP £30,000 (Public list prices)



A comparison of the average number of key events by treatment strategy is presented in Table 37. These are aligned with the NMA results with alemtuzumab having the fewest relapses (i.e., lowest estimated rate of ARR) and Interferon-beta-1b SC 250µg having the fewest increases in EDSS (i.e., lowest estimated rate of CDP6).

Table 37 Average number of key events (relapses, increases in severity, decreases in severity , serious adverse events) by treatment

Treatments	Relapses	Increase in EDSS	Decrease in EDSS	Serious adverse events
Natalizumab-IV	1.71	1.84	1.33	4.47
Natalizumab-SC	1.70	1.84	1.33	4.40
Natalizumab biosimilar-IV	1.79	1.85	1.34	4.47
Natalizumab biosimilar-SC	1.85	1.83	1.31	4.42
Fingolimod	1.85	1.94	1.31	4.44
Alemtuzumab	1.64	1.74	1.32	4.45
Cladribine	1.87	2.08	1.35	4.45
Ponesimod	2.13	1.95	1.34	4.46
Ofatumumab	1.94	1.85	1.33	4.46
Ocrelizumab	1.73	1.82	1.33	4.47
Peginterferon -β-1a SC 125µg	2.03	1.84	1.32	4.45
Interferon-beta-1a SC 22µg	2.07	1.96	1.32	4.48
Interferon-beta-1a SC 44µg	2.03	1.93	1.32	4.45
Interferon-beta-1a IM 30µg	2.14	1.96	1.33	4.44
Interferon-beta-1b SC 250µg	2.05	1.71	1.33	4.45
Glatiramer Acetate 20mg	2.07	1.96	1.32	4.49

6.8.4 Sensitivity analyses

The incremental net benefits from the sensitivity analyses at £20,000/QALY are presented in Table 38 and at £30,000/QALY in Table 39. We used 100 samples and 100 patients for these simulations.

These sensitivities again find that natalizumab-IV has lower net benefit at £20-30,000/QALY than natalizumab biosimilar-IV with very little impact on the mean results.

Interferon-beta-1b SC 250µg, glatiramer Acetate 20mg and 40mg, , and interferon-beta-1a SC 44µg all have the greatest net benefits under all sensitivities except that using the HA RRMS fixed effects NMA which did not include these treatments. In this sensitivity Peginterferon-β-1 SC 125µg was the most cost-effective treatment.

Table 38 Incremental net benefits relative to natalizumab-IV at £20,000/QALY for the base case and sensitivity analyses (publicly available list prices)

Treatment	Base case	Scenario 1 (All RRMS MS Registry population)	Scenario 2 (base-case w/ random effects NMA)	Scenario 3 (base-case & assuming JCV testing provided free of charge by manufacturers)	Scenario 4 (using lowest price generics for comparators)	Scenario 5 (base case & assuming a reduction in Natalizumab-SC administration costs)	Scenario 6 (base-case w/ HA RRMS fixed effects NMA)	Scenario 7 (mortality by severity Sadovnik et al cited in Pokorski et al)
Natalizumab-SC	-502.64 (-16551.93, 16092.39)	-1175.66 (-29669.24, 28607.08)	1359.43 (-36328.44, 38114.99)	1120.00 (-28045.23, 35469.04)	-3580.92 (-48641.36, 39502.73)	27363.98 (-4981.51, 63508.21)	4025.91 (-26535.10, 29614.07)	-2774.56 (-36925.79, 27693.24)
Natalizumab biosimilar-IV	9206.89 (-7313.60, 27383.20)	9499.06 (-24684.71, 41320.41)	7102.31 (-23755.19, 41940.17)	7079.84 (-21867.85, 38797.35)	9718.90 (-46081.25, 51471.25)	8797.24 (-19756.75, 41330.99)	14170.51 (-13374.03, 43965.83)	6493.81 (-23549.58, 37749.31)
Fingolimod	19328.78 (1875.72, 42263.48)	18018.54 (-9602.02, 49531.56)	19924.56 (-16512.89, 60634.14)	18181.83 (-14724.38, 54010.56)	118042.12 (46261.41, 192351.24)	19905.32 (-12768.52, 55194.94)	20058.35 (-13833.63, 54979.91)	15599.07 (-18267.32, 55662.61)
Alemtuzumab	53401.40 (-7103.10, 126307.28)	44747.92 (-1511.32, 91180.37)	46955.48 (-33640.26, 123878.87)	52465.45 (-19867.76, 130430.13)	67921.59 (-19696.45, 180663.64)	54040.11 (-18431.06, 131261.57)	53558.38 (-11572.85, 134806.42)	50952.05 (-22023.64, 128840.80)
Cladribine	69589.03 (12588.27, 140227.70)	55955.31 (17609.23, 104260.30)	72025.41 (1912.41, 134501.24)	68203.10 (6351.63, 142132.52)	71355.34 (113.50, 156532.62)	69902.30 (7729.55, 142483.83)	71422.40 (7929.58, 148112.75)	66738.85 (-1677.44, 139325.81)
Ponesimod	56971.32 (27400.25, 92534.88)	51503.46 (26019.57, 77823.96)	54819.16 (11672.90, 100063.01)	55670.32 (13710.85, 96627.98)	55628.68 (569.73, 103429.50)	57333.40 (14758.64, 98152.76)	60054.02 (19541.63, 106405.01)	54839.13 (15218.50, 95861.20)
Ofatumumab	10145.61 (-5193.92, 25898.05)	11683.70 (-16435.44, 43285.10)	4184.45 (-27290.51, 39214.25)	8978.62 (-21116.94, 49286.21)	7021.89 (-53034.39, 45657.09)	10541.94 (-19294.77, 50356.35)	12452.77 (-19464.27, 45988.31)	6481.58 (-30447.35, 39763.47)
Ocrelizumab	-1481.02 (-16697.29, 12669.42)	514.03 (-29012.99, 29018.72)	-4110.19 (-33888.14, 30206.89)	-4452.28 (-28593.01, 27464.69)	-2928.55 (-41947.04, 37742.87)	-2865.90 (-26606.58, 29503.30)	25.29 (-23364.00, 21622.08)	-1175.70 (-33470.28, 32022.61)

Treatment	Base case	Scenario 1 (All RRMS MS Registry population)	Scenario 2 (base-case w/ random effects NMA)	Scenario 3 (base-case & assuming JCV testing provided free of charge by manufacturers)	Scenario 4 (using lowest price generics for comparators)	Scenario 5 (base case & assuming a reduction in Natalizumab-SC administration costs)	Scenario 6 (base-case w/ HA RRMS fixed effects NMA)	Scenario 7 (mortality by severity Sadovnik et al cited in Pokorski et al)
Peginterfero-beta-1 SC 125µg	103897.42 (53635.73, 162561.20)	95123.23 (61515.56, 125958.99)	123452.38 (76219.86, 177565.24)	100137.69 (52702.80, 162536.57)	117030.20 (41577.74, 197666.80)	101781.37 (53686.69, 163941.10)	105745.13 (46897.88, 169562.95)	100299.78 (39644.42, 160243.93)
Interferon-beta-1a SC 22µg	91672.47 (43468.36, 146183.52)	82079.58 (44477.46, 116689.35)	86792.81 (24665.13, 147722.50)	90084.12 (35019.59, 150623.25)	95086.57 (22695.47, 168649.05)	91711.02 (37505.95, 151949.17)	96461.23 (48282.03, 160457.24)	89332.05 (32675.62, 141115.21)
Interferon-beta-1a SC 44µg	104070.37 (52949.57, 164025.84)	94673.34 (57147.33, 137462.03)	97255.22 (41522.95, 161920.30)	102459.19 (43566.72, 159032.65)	111688.57 (35194.35, 204976.04)	104028.08 (44060.84, 162119.67)	107617.60 (51851.91, 174931.03)	100831.69 (34336.55, 160565.53)
Interferon-beta-1a IM 30µg	100786.61 (50753.11, 158377.71)	90829.44 (55720.52, 127294.28)	99075.61 (33740.79, 164003.16)	98558.74 (47394.05, 156510.80)	105655.76 (33450.48, 187345.92)	100142.05 (48621.56, 157084.04)	103200.62 (44398.89, 173012.06)	96251.87 (33203.88, 154383.25)
Interferon-beta-1b SC 250µg	112627.43 (59720.87, 171813.41)	106828.65 (72206.63, 140323.84)	111042.81 (56490.33, 177681.16)	112455.56 (48584.83, 171933.81)	131192.70 (57185.49, 210373.76)	114100.12 (50055.47, 174599.81)	116434.76 (54429.28, 180999.23)	114236.92 (55747.69, 170927.70)
Glatiramer Acetate 20mg	110232.01 (56926.28, 171622.40)	102860.07 (67992.32, 138802.08)	108224.11 (40644.96, 166954.72)	107401.61 (51351.72, 167515.79)	120812.17 (39933.54, 196247.18)	108979.70 (51781.39, 170327.73)	112842.84 (56889.29, 185352.83)	106787.19 (33761.02, 162576.62)
Glatiramer Acetate 40mg	110170.24 (55732.39, 173179.13)	102976.61 (61727.65, 140501.29)	106629.20 (43444.00, 171531.81)	107527.87 (54679.26, 173795.38)	124142.56 (51563.30, 193655.20)	109193.38 (55282.65, 176678.09)	112163.55 (54903.16, 177224.57)	108720.45 (45912.86, 164854.70)

Treatment	Scenario 8 (clinical equivalence: natalizumab and natalizumab biosimilar)	Scenario 9 (EID for natalizumab and natalizumab biosimilar)	Scenario 10 (OPERA edss 0-7 and Orme utilities edss 8-9 for RRMS & SPMS)	Scenario 11 (CLARITY edss 0-6 and Orme utilities edss 7-9 for RRMS & SPMS)	Scenario 12 (TA127 for carer disutilities)	Scenario 13 (mortality by severity edss<4 Jick et al and edss≥4 Harding et al)	Scenario 14 (NMA where CPD3 is used for studies with missing CDP6)	Scenario 15 /16 (cPAS analysis only)
Natalizumab-SC	-1278.18 (-38191.80, 35591.77)	1485.83 (-27061.77, 31106.46)	750.41 (-32502.18, 37058.72)	2567.06 (-42033.49, 40642.75)	1091.43 (-26668.71, 33614.22)	2838.40 (-30643.36, 38291.35)	-2225.69 (-35083.01, 30834.21)	
Natalizumab biosimilar-IV	10019.51 (-26133.04, 44602.47)	6735.60 (-21594.60, 32675.59)	8266.95 (-22110.61, 39312.40)	9223.86 (-25804.48, 50074.35)	8650.77 (-20722.07, 39292.74)	10924.10 (-23255.35, 43909.48)	10110.35 (-23720.92, 39402.21)	
Fingolimod	17336.97 (-20708.42, 48974.61)	-20669.22 (-52333.20, 12706.90)	19244.90 (-14860.22, 54782.39)	19425.21 (-17476.14, 57573.48)	19812.01 (-10914.58, 53724.28)	19884.82 (-10668.25, 58825.94)	21297.02 (-9356.68, 57166.78)	
Alemtuzumab	54148.43 (-24999.64, 134328.00)	13173.14 (-46258.43, 68226.88)	53977.89 (-19917.96, 137459.13)	54402.40 (-24169.52, 130365.69)	53810.58 (-17515.41, 132116.44)	52611.61 (-11356.91, 124188.18)	52699.80 (-9781.26, 129818.88)	
Cladribine	69179.72 (-453.15, 144585.44)	29265.45 (-17618.27, 83934.81)	69638.53 (4417.53, 142042.53)	69533.83 (2505.11, 146531.27)	69999.09 (9351.71, 143480.08)	69157.88 (6849.67, 133452.62)	72924.50 (11855.26, 144001.93)	
Ponesimod	56685.23 (9927.90, 107065.19)	16803.04 (-12725.34, 45357.68)	56507.00 (15052.59, 98283.10)	56157.43 (6886.37, 104438.10)	57729.97 (18125.63, 95528.43)	56762.04 (18878.21, 101727.51)	57028.41 (22472.35, 100369.92)	
Ofatumumab	11031.36 (-19408.21, 45097.93)	-30124.79 (-68029.24, 1472.75)	10229.24 (-22218.91, 50713.15)	10617.77 (-27666.65, 48446.21)	10367.02 (-18008.74, 48579.58)	11342.07 (-15601.67, 40067.58)	10747.23 (-26716.03, 45611.63)	
Ocrelizumab	-2867.48 (-33689.97, 30027.05)	-43194.29 (-79319.44, -3112.75)	-2815.69 (-28578.69, 28925.15)	-2391.33 (-34872.80, 36688.42)	-2711.34 (-30696.09, 24924.77)	322.76 (-26462.82, 29913.22)	-2029.40 (-29440.74, 30725.96)	

Treatment	Scenario 8 (clinical equivalence: natalizumab and natalizumab biosimilar)	Scenario 9 (EID for natalizumab and natalizumab biosimilar)	Scenario 10 (OPERA edss 0-7 and Orme utilities edss 8-9 for RRMS & SPMS)	Scenario 11 (CLARITY edss 0-6 and Orme utilities edss 7-9 for RRMS & SPMS)	Scenario 12 (TA127 for carer disutilities)	Scenario 13 (mortality by severity edss<4 Jick et al and edss≥4 Harding et al)	Scenario 14 (NMA where CPD3 is used for studies with missing CDP6)	Scenario 15 /16 (cPAS analysis only)
Peginterfero-beta-1 SC 125µg	105577.91 (40850.35, 172715.68)	61441.60 (24662.55, 107195.98)	101036.56 (53267.60, 163257.91)	102634.09 (45428.75, 167455.26)	101966.55 (53900.39, 161698.97)	103007.88 (40457.77, 161354.89)	105649.42 (50822.37, 165161.75)	
Interferon-beta-1a SC 22µg	91079.37 (28180.45, 145848.17)	51418.61 (12240.19, 98008.36)	91189.62 (34448.50, 154915.25)	90996.90 (30867.05, 155301.26)	91773.16 (39404.01, 149874.27)	90142.05 (34329.77, 153166.14)	92970.42 (42681.31, 151229.16)	
Interferon-beta-1a SC 44µg	103044.38 (39513.18, 165563.19)	63405.01 (15911.20, 100737.74)	103497.92 (45891.75, 158934.82)	105017.07 (44366.71, 167754.76)	104060.56 (46053.76, 160570.29)	102783.92 (45157.76, 163503.11)	103377.00 (52732.49, 171142.16)	
Interferon-beta-1a IM 30µg	101071.83 (46599.30, 166303.85)	59406.91 (22796.83, 101617.24)	99529.73 (46432.64, 157012.09)	100547.17 (46084.80, 159366.98)	100062.55 (50430.56, 154370.62)	100736.69 (45052.89, 153971.22)	97017.53 (41649.49, 161031.89)	
Interferon-beta-1b SC 250µg	112592.85 (46336.25, 185107.75)	73625.82 (27573.53, 115688.33)	113552.74 (49697.17, 175625.62)	114204.10 (44068.00, 181399.20)	113426.77 (53983.42, 173119.33)	112493.92 (52915.35, 166440.65)	102675.68 (52204.37, 174544.31)	
Glatiramer Acetate 20mg	109675.23 (49952.42, 176035.11)	68402.79 (23810.41, 111748.30)	108312.46 (51061.66, 172657.03)	109515.17 (43045.63, 170853.86)	109474.95 (53972.54, 167663.22)	108321.91 (51623.78, 165893.30)	108813.80 (42989.19, 164738.64)	
Glatiramer Acetate 40mg	110631.27 (47819.81, 178301.13)	68888.11 (28822.79, 114070.13)	108891.79 (56543.53, 176877.29)	109406.43 (48782.37, 185041.33)	109450.65 (57368.58, 177744.91)	109771.54 (57719.87, 166873.15)	110029.91 (56087.12, 177777.51)	

Table 39 Incremental net benefits relative to natalizumab-IV at £30,000/QALY for the base case and sensitivity analyses (publicly available list prices)

Treatment	Base case	Scenario 1 (All RRMS MS Registry population)	Scenario 2 (base-case w/ random effects NMA)	Scenario 3 (base-case & assuming JCV testing provided free of charge by manufacturers)	Scenario 4 (using lowest price generics for comparators)	Scenario 5 (base case & assuming a reduction in Natalizumab-SC administration costs)	Scenario 6 (base-case w/ HA RRMS fixed effects NMA)	Scenario 7 (mortality by severity Sadovnik et al cited in Pokorski et al)
Natalizumab-SC	-522.09 (-17946.95, 16796.23)	-689.97 (-35012.68, 35627.60)	1557.38 (-42171.91, 43922.79)	1556.64 (-38171.72, 42532.31)	-4261.09 (-59486.25, 46357.82)	27800.62 (-11463.64, 69079.92)	5570.41 (-29063.99, 39850.03)	-3496.13 (-47367.48, 37291.59)
Natalizumab biosimilar-IV	9144.24 (-8856.05, 28394.97)	9791.36 (-32724.49, 48252.05)	7002.58 (-28527.71, 49753.73)	7143.44 (-26571.60, 44047.86)	9484.61 (-57670.01, 62077.55)	8860.84 (-23429.58, 45826.31)	15794.78 (-18963.93, 53607.01)	4988.47 (-30812.17, 46560.50)
Fingolimod	18348.37 (-1154.99, 42675.66)	16724.02 (-17247.34, 52242.35)	20474.33 (-28169.37, 74335.92)	17343.34 (-25589.59, 62350.14)	117135.13 (34575.31, 203145.45)	19066.83 (-24274.07, 62809.87)	20009.01 (-26861.51, 61382.49)	13040.23 (-27031.39, 56818.44)
Alemtuzumab	53920.54 (-8390.93, 128553.65)	45665.52 (-7901.53, 98292.37)	45183.27 (-47409.79, 126582.80)	53652.37 (-29887.38, 129367.22)	68728.76 (-32147.70, 188493.59)	55227.02 (-28382.46, 130048.10)	54576.15 (-19888.19, 140725.96)	50578.14 (-29081.97, 129805.14)
Cladribine	67008.48 (9544.84, 140804.95)	52405.88 (12249.46, 106487.11)	71123.83 (2750.53, 136780.76)	66498.89 (-3171.24, 141596.78)	66983.34 (-9195.41, 156437.61)	68198.10 (-1821.52, 142994.28)	70116.23 (969.29, 150307.68)	63082.04 (-9321.53, 139652.63)
Ponesimod	55408.96 (23033.04, 92103.02)	49212.01 (21530.37, 82182.49)	52422.93 (-2385.56, 102918.51)	54820.23 (4848.93, 103391.65)	52629.65 (-13284.84, 108561.92)	56483.30 (5990.45, 103918.05)	59827.99 (12531.79, 113444.96)	52600.02 (5291.55, 93853.99)
Ofatumumab	10280.50 (-8162.22, 28179.71)	12076.59 (-21363.34, 47176.45)	1771.24 (-44359.56, 47921.54)	9082.91 (-30286.57, 59553.25)	6272.72 (-67504.36, 56453.91)	10646.22 (-28414.85, 59859.93)	13209.62 (-25029.75, 54920.65)	4707.33 (-43096.57, 46447.40)
Ocrelizumab	-1179.85 (-19531.68, 15710.44)	1530.81 (-39351.12, 37679.91)	-4416.91 (-42138.89, 42823.15)	-3538.41 (-36809.65, 40386.59)	-2965.33 (-51686.98, 45225.32)	-1952.03 (-35764.97, 42425.19)	1783.91 (-28868.13, 29178.03)	-475.86 (-45292.32, 39927.93)

Treatment	Base case	Scenario 1 (All RRMS MS Registry population)	Scenario 2 (base-case w/ random effects NMA)	Scenario 3 (base-case & assuming JCV testing provided free of charge by manufacturers)	Scenario 4 (using lowest price generics for comparators)	Scenario 5 (base case & assuming a reduction in Natalizumab-SC administration costs)	Scenario 6 (base-case w/ HA RRMS fixed effects NMA)	Scenario 7 (mortality by severity Sadovnik et al cited in Pokorski et al)
Peginterferon-beta-1 SC 125µg	103668.48 (51467.09, 161755.27)	94533.17 (54183.28, 133303.14)	130993.98 (70393.71, 186313.61)	99563.37 (45097.25, 168486.96)	116868.59 (32495.16, 200263.39)	101207.05 (46081.14, 169891.48)	106516.08 (39591.39, 180739.00)	99009.88 (30636.65, 160225.34)
Interferon-beta-1a SC 22µg	90061.60 (38607.49, 147656.29)	80243.16 (39373.55, 123505.27)	83473.19 (11223.17, 154678.54)	89595.85 (30700.74, 156596.20)	92243.55 (12978.96, 176142.80)	91222.75 (32932.21, 157922.11)	96880.00 (40784.03, 172045.76)	87128.17 (25732.56, 153362.55)
Interferon-beta-1a SC 44µg	102737.37 (49237.91, 163673.72)	93051.80 (50608.56, 143025.17)	93229.15 (27678.55, 157470.33)	101633.52 (37175.14, 160986.50)	109695.45 (17958.00, 209220.00)	103202.41 (38203.13, 164008.95)	107645.09 (41429.52, 179396.40)	98726.28 (33229.09, 158912.18)
Interferon-beta-1a IM 30µg	99340.88 (47499.75, 159353.18)	89140.44 (47906.83, 133758.54)	97424.93 (24837.79, 171473.09)	97005.54 (40883.31, 160555.10)	102349.54 (24605.69, 190391.77)	98588.85 (41791.64, 161204.59)	102938.84 (35934.41, 178537.65)	93095.02 (21475.53, 160730.55)
Interferon-beta-1b SC 250µg	113572.06 (58682.25, 174340.67)	108740.24 (65353.84, 152998.45)	111568.58 (48100.77, 180399.32)	114719.22 (48273.21, 177032.98)	133437.95 (50284.80, 213860.85)	116363.78 (49716.67, 179104.58)	118328.15 (50875.44, 191684.05)	115590.23 (56788.59, 169821.51)
Glatiramer Acetate 20mg	108876.34 (54279.66, 170529.85)	101360.13 (62213.42, 150307.95)	106416.74 (27009.86, 167845.21)	106237.71 (44363.32, 169220.80)	118314.61 (23380.07, 198729.87)	107815.81 (45460.86, 171962.81)	112226.57 (51767.17, 193019.93)	104474.45 (27961.17, 167248.65)
Glatiramer Acetate 40mg	108841.21 (52428.23, 175299.49)	101662.62 (52413.41, 144011.18)	104500.18 (28908.84, 176144.52)	106812.40 (48969.68, 176702.99)	122994.90 (45329.48, 197172.35)	108477.91 (49475.10, 179585.70)	111798.63 (55097.23, 182718.08)	107179.90 (35206.92, 163692.42)

Treatment	Scenario 8 (clinical equivalence: natalizumab and natalizumab biosimilar)	Scenario 9 (EID for natalizumab and natalizumab biosimilar)	Scenario 10 (OPERA edss 0-7 and Orme utilities edss 8-9 for RRMS & SPMS)	Scenario 11 (CLARITY edss 0-6 and Orme utilities edss 7-9 for RRMS & SPMS)	Scenario 12 (TA127 for carer disutilities)	Scenario 13 (mortality by severity edss<4 Jick et al and edss≥4 Harding et al)	Scenario 14 (NMA where CPD3 is used for studies with missing CDP6)	Scenario 15 /16 (cPAS analysis only)
Natalizumab-SC	-2261.73 (-51070.00, 40644.89)	1922.47 (-35296.82, 39605.21)	1008.57 (-38483.07, 42717.27)	3733.54 (-54139.20, 53067.15)	1520.11 (-35764.46, 39443.44)	2165.23 (-40843.21, 42566.04)	-2620.98 (-45858.21, 34333.87)	
Natalizumab biosimilar-IV	9998.97 (-36573.62, 54874.09)	6799.20 (-26935.93, 41991.20)	8139.82 (-27978.55, 48557.82)	9575.19 (-42244.48, 68901.52)	8715.56 (-25871.52, 43387.27)	10911.20 (-33343.72, 52300.22)	10777.82 (-34589.17, 48297.98)	
Fingolimod	15823.20 (-31564.40, 55984.75)	-21507.71 (-61150.14, 19727.14)	18154.08 (-25159.54, 63812.99)	18424.55 (-29182.79, 69543.51)	19004.75 (-21028.64, 60398.94)	18379.35 (-20049.25, 60705.65)	21119.03 (-13883.68, 57893.33)	
Alemtuzumab	54734.46 (-33504.04, 144635.09)	14360.05 (-53305.20, 70893.75)	55129.19 (-25350.46, 140341.36)	55765.97 (-41644.01, 137370.14)	54878.24 (-22665.76, 131523.53)	52729.73 (-16236.82, 125247.12)	53304.10 (-16887.14, 129898.04)	
Cladribine	66447.13 (-11547.56, 143613.60)	27561.24 (-30662.13, 86430.07)	67865.54 (-4923.60, 144601.21)	67708.49 (-18312.26, 148762.94)	68406.38 (388.42, 142455.69)	66412.47 (2249.52, 128953.25)	72030.12 (4510.79, 148992.09)	
Ponesimod	54937.62 (-1235.12, 113151.71)	15952.94 (-22171.94, 51787.99)	55288.68 (4748.73, 105110.53)	54764.32 (-8246.83, 115369.90)	57123.14 (12614.58, 101566.43)	54374.14 (9321.32, 104494.20)	55594.78 (12170.46, 102122.60)	
Ofatumumab	11431.03 (-29329.86, 57790.51)	-30020.51 (-77195.95, 14232.93)	10169.11 (-32714.97, 61417.70)	10751.90 (-45763.18, 62860.37)	10375.78 (-29466.51, 52678.30)	10748.09 (-28353.97, 48245.77)	11075.22 (-37007.43, 50117.10)	
Ocrelizumab	-3234.23 (-41907.92, 39657.92)	-42280.42 (-84375.83, 7245.06)	-1868.75 (-34280.33, 41638.06)	-1232.21 (-45682.07, 51094.94)	-1712.24 (-33300.19, 34626.96)	310.03 (-34191.59, 39395.47)	-1167.58 (-37704.18, 37862.97)	

Treatment	Scenario 8 (clinical equivalence: natalizumab and natalizumab biosimilar)	Scenario 9 (EID for natalizumab and natalizumab biosimilar)	Scenario 10 (OPERA edss 0-7 and Orme utilities edss 8-9 for RRMS & SPMS)	Scenario 11 (CLARITY edss 0-6 and Orme utilities edss 7-9 for RRMS & SPMS)	Scenario 12 (TA127 for carer disutilities)	Scenario 13 (mortality by severity edss<4 Jick et al and edss≥4 Harding et al)	Scenario 14 (NMA where CPD3 is used for studies with missing CDP6)	Scenario 15 /16 (cPAS analysis only)
Peginterfero-beta-1 SC 125µg	105455.16 (27674.70, 178584.11)	60867.27 (13980.11, 112468.92)	100126.41 (47383.06, 167978.90)	102522.71 (30611.17, 181005.58)	101521.39 (46266.06, 165198.67)	102189.74 (31933.69, 161143.06)	106062.85 (45805.94, 167778.88)	
Interferon-beta-1a SC 22µg	89224.96 (19680.79, 156795.39)	50930.34 (3405.90, 103994.53)	90470.52 (30930.72, 161942.39)	90181.44 (16867.31, 164450.34)	91345.82 (35955.36, 151989.71)	87265.88 (25230.60, 160637.77)	92421.85 (35903.14, 154083.68)	
Interferon-beta-1a SC 44µg	100815.15 (31670.94, 167690.88)	62579.33 (6602.38, 107114.68)	102402.02 (36443.18, 157964.66)	104680.75 (28576.44, 174641.47)	103245.99 (38465.64, 162690.97)	101245.82 (36826.06, 170015.32)	102533.03 (50838.74, 168289.14)	
Interferon-beta-1a IM 30µg	99700.33 (38093.34, 169275.01)	57853.71 (10378.77, 104884.19)	97671.99 (42088.84, 161689.78)	99198.15 (30403.63, 165066.93)	98471.22 (45849.76, 155899.62)	99197.28 (36149.08, 158677.49)	94454.46 (32960.76, 159193.95)	
Interferon-beta-1b SC 250µg	112983.87 (35796.55, 193902.76)	75889.47 (20170.21, 119200.28)	115579.54 (46495.10, 180117.54)	116556.58 (23293.14, 189092.42)	115390.58 (54764.27, 176742.79)	112716.72 (52674.22, 172587.31)	99875.75 (42387.95, 179035.44)	
Glatiramer Acetate 20mg	107739.41 (42971.46, 175151.42)	67238.90 (19214.36, 113770.83)	106815.07 (42998.65, 175453.48)	108619.13 (30126.60, 172470.21)	108558.80 (45674.51, 168272.54)	105709.95 (40351.22, 176708.21)	107386.22 (35824.39, 163214.27)	
Glatiramer Acetate 40mg	109682.94 (37901.26, 176329.95)	68172.64 (19741.67, 117589.56)	108071.42 (48667.77, 182454.74)	108843.38 (34791.31, 196504.67)	108909.72 (52681.72, 181766.29)	107772.66 (54535.87, 167691.58)	108794.41 (56257.85, 182793.90)	

6.8.5 Value of information analysis

The results of the value of information analysis are presented in Table 40. These show that the EVPPI is greatest for the NMA treatment effects on efficacy (ARR and CDP6) and safety (SAEs and discontinuation). This indicates that the greatest decision uncertainty is associated with the NMA estimates and RCT data. Utilities have a greater EVPPI than costs but both are important factors with a high EVPPI relative to total EVPI. Baseline rates of EDSS increase/decrease, progression to SPMS, and relapse rates have high and similar EVPPI. Absolute discontinuation rate and SAE rate have low EVPPI and their uncertainty thus has limited impact on the decision.

Table 40 Value of Information analysis results for the HARRMS base case using BART* method (publicly available list prices)

Parameter group	Per-person EVPPI at £20,000/QALY	Per-person EVPPI at £30,000/QALY
Total EVPI	2909.91	3351.91
NMA on CDP6	1651.27	1638.17
NMA on ARR	1627.80	1602.88
NMA on SAEs	1557.91	1050.78
NMA on discontinuation	758.39	543.88
Costs	754.67	471.40
Utilities	61.95	25.18
MS registry EDSS increase/decrease	91.43	43.95
MS registry SPMS progression	2909.91	3351.91
MS registry ARR	1651.27	1638.17
Discontinuation rate	1627.80	1602.88
SAEs rate	1557.91	1050.78

*BART=Bayesian additive regression trees

6.8.6 Summary of findings of economic evaluation

With the exception of ocrelizumab, all treatments had greater net benefit at £20-30,000/QALY than natalizumab-IV, natalizumab biosimilar-IV and natalizumab-SC. The natalizumabs also had close to 0% chance of having highest net benefit at £20,000/QALY and £30,000/QALY. Costs were generally higher on natalizumab than other treatments, though there was no difference in QALYs with 95% CrI completely overlapping.

Natalizumab-IV has lower mean net benefit at £20-30,000/QALY than natalizumab biosimilar-IV, although the 95% CrI overlap. Natalizumab-SC has very similar mean net benefit to Natalizumab-IV. The natalizumab biosimilar-IV has lower costs but also lower QALYs than natalizumab-IV but the 95% CrI for both are overlapping suggesting no evidence of a difference. Natalizumab-SC has very similar costs and QALYs to natalizumab-IV, again with no evidence of a difference.

Across treatments, interferon-beta-1b SC 250µg has the greatest net monetary benefit at £20-30,000/QALY, followed by glatiramer Acetate 20mg, glatiramer acetate 40mg,

interferon-beta-1a SC 44µg, and peginterferon -β-1 SC 125µg. However, the probability that any one of them has the greatest net benefit is below 50%, indicating uncertainty as to which is most cost-effective.

Results were robust to sensitivity analyses relating to MS registry baseline estimates, use of random effects NMA, use of HA RRMS NMA, excluding the price of JCV testing for branded natalizumab, reducing the natalizumab-SC treatment administration costs, stratifying mortality by EDSS severity, assuming equivalent efficacy between natalizumab and its biosimilar, using EID for natalizumab and its biosimilar, exploring alternative sources for utilities, and using an NMA with CDP3 where CDP6 is not reported. In the sensitivity using the HA RRMS NMA, glatiramer acetate and Interferon-beta-1b SC 250µg were not included. However, natalizumab-IV and natalizumab-SC were not cost-effective compared to any included treatment and the most cost-effective treatment was peginterferon -β-1 SC 125µg.

Value of information analysis found that the parameters with greatest impact on the results were the NMA hazard ratios on ARR, CDP6, SAEs, and discontinuation. However, many parameters, including costs, utilities, and MS registry rates, had substantial impact on the results indicating high parameter uncertainty.

7 Assessment of factors relevant to the NHS and other parties

New diagnostic criteria for MS reported at the recent ECDMS conference may allow earlier diagnosis, and hence also treatment, of people with MS. This will have implications for the NHS. The lack of a consensus definition on HARRMS make it challenging to introduce treatments for this population. There is a need for a clear and consistent definition of the HARRMS population to allow treatments to be prescribed appropriately.

Evolving formulation availability will affect delivery options and some Trusts may make decisions based on support from pharmaceutical companies. For example, in-home delivery of infusions by nurses supplied by companies. However, this could raise a vulnerability with shifts in demand if these are subsequently withdrawn, particularly if done at relatively short notice.

8 DISCUSSION

8.1 Statement of principal findings

Based on findings from our NMA and SLR, most interventions reduced relapses and the proportion of participants with MRI lesions compared to placebo. Alemtuzumab, cladribine, ocrelizumab, natalizumab, fingolimod and peginterferon beta 1a also reduced disease progression compared to placebo. There were no differences in any AEs, serious AEs or treatment related AEs for any intervention compared to placebo. Fingolimod, glatiramer acetate, interferon beta 1a, interferon beta 1b and peginterferon beta 1a were associated with increased treatment discontinuation. There was little evidence for a difference in quality of life. There was no evidence of a difference between natalizumab and natalizumab biosimilar for relapse rates, MRI lesions or AEs. Data in HARRMS were available for fingolimod, ocrelizumab, alemtuzumab, cladribine, beta-interferon, AHSCT, and placebo. We also included one study on natalizumab conducted in a population that was close to our definition of HARRMS. All interventions except interferon beta 1a were associated with reduced relapse risk compared to placebo; there were little data for other outcomes.

Compared with natalizumab-IV, natalizumab biosimilar-IV and natalizumab-SC, all treatments had greater net benefit at £20-30,000/QALY, with the only exception being ocrelizumab which had lower net benefits. Costs were generally higher on natalizumab than other treatments, though there was no difference in QALYs with 95% CrI completely overlapping. The results and conclusions were unchanged under all sensitivities. Value of information analysis found that the greatest contributor to decision uncertainty was the effectiveness of treatments.

8.1.1 Findings on clinical effectiveness

We identified 42 studies that fulfilled inclusion criteria for our SLR. However, the majority of the evidence was in the general RRMS population rather than those with highly active disease, and most studies evaluated comparator interventions rather than the technologies of interest for this appraisal - natalizumab (Tysabri, Biogen) and natalizumab biosimilar (Tyruko, Sandoz).

ARR was the most frequently reported outcome across studies, with 39 of the 40 trials in the general RRMS population reporting data for this outcome. ARR data generally suggested that newer DMT, such as alemtuzumab, ocrelizumab, and natalizumab, are more effective than older treatments like interferon beta and glatiramer acetate, which showed limited improvements over placebo. Fewer than half the included studies provided data on the proportion of participants who had Gd+ (19 studies) or new or enlarging T2 lesions (17 studies) but data were consistent with the findings for ARR, suggesting a greater effect for newer DMT. Disease progression was also reported in less than half of studies, and we were unable to connect studies of teriflunomide, ponesimod, and ofatumumab to the main network. These studies were therefore not included in the NMA for these outcomes. Data for the remaining interventions were also consistent with the findings for ARR, suggesting a greater effect of newer DMT on reducing disease progression, with slightly stronger evidence on an effect for CDP3. Disability progression can be highly variable across individuals, with some showing gradual decline followed by periods of improvement rather than consistent decline over relatively short time periods, with decline only becoming

evidence over longer time periods. This can make it difficult for patients to meet the criteria for confirmed disability progression, particularly CDP6 which requires sustained progression over 6 months, over shorter follow-up periods (e.g., 6 months). The use of sustained disability metrics, such as 6-month confirmed disability progression (CDP6), offers a more reliable measure of true progression than CDP3, as it reflects long-term changes rather than temporary fluctuations. However, true disability progression often unfolds over years or even decades, making it challenging to observe in standard clinical trials with shorter follow-up periods.[178, 179]

All but two of the trials included in this review provided data on AEs, a further two only reported data on specific AEs of interest and so could not be included in our synthesis as they did not report at least one the AEs measures of interest for this appraisal (incidence of any AEs, SAEs, treatment related AEs, of treatment discontinuation due to AEs). There was no evidence of an increased risk of any AEs or treatment related AEs for any of the interventions evaluated. It may be difficult to determine the true impact of AEs from the outcome "any AE" as this is defined very broadly so that any potential adverse events, including those not thought to be related to the intervention, are recorded as potential AEs. Close to 100% of participants in both groups experienced AEs and so this measure does not distinguish between groups. There were less data on treatment related AEs which were only reported for eight studies. These may be expected to be a more appropriate measure of the true risk of AEs associated with the different interventions, but there was also little evidence of a difference between groups for this measure. There was a suggestion that natalizumab and peginterferon beta 1a were associated with a lower risk of SAEs compared to placebo, but CrIs were wide and included 1. Fingolimod, glatiramer acetate (SC20), interferon beta 1a (SC44) and peginterferon beta 1a were associated with a higher rate of treatment discontinuation than placebo; there was no evidence of a difference between other interventions and placebo. However, SAEs are generally rare and so require large sample sizes to show difference in risk between groups. Analyses of real-world data may be necessary to identify the potential risk of these.[180]

There was limited evidence on the technologies of interest for this appraisal - natalizumab and natalizumab biosimilar. We identified only four studies of these interventions. This included two placebo control trials of natalizumab – AFFIRM, a large multinational trial (n=943) with 24 months follow-up, and Saida 2017 which only included 94 participants, had a short follow-up period of 6 months and only included Japanese participants. An additional trial (REVEAL) compared natalizumab with fingolimod. This phase 4 randomised study, with a planned overall duration of 68 weeks was terminated prematurely due to slow enrolment and so data were only available for 12 months follow-up. The fourth trial was a direct comparison between natalizumab and natalizumab biosimilar – the only randomised evidence available for this intervention. This trial also had a short follow-up period (24 weeks) and its primary outcomes were MRI findings (new gadolinium-enhancing T1-weighted lesions and new/enlarging T2-weighted lesions). However, two previous meta-analyses [181, 182] have found a correlation between the effect of MS drugs on relapses and MRI activity, with the magnitude of the benefit on MRI lesions predicting the magnitude of the effect on relapse rates. All four trials were conducted in the general RRMS population and did not provide any data specifically in patients with HARRMS. However, the Saida 2017 study included a very high proportion (88%) of previously treated participants and required

that participants had experienced at least one relapse in the preceding year, and so was close to our definition of at least 90% of participants having HARRMS. Overall, the available data suggested no evidence of a difference between natalizumab and its biosimilar in terms of annualized relapse rate (ARR), the proportion of participants with MRI-detected lesions or AEs. There were no data on disease progression for patients treated with natalizumab biosimilar, although natalizumab was associated with a greater reduction in CDP3 and CDP6 compared to placebo.

All trials of natalizumab evaluated natalizumab administered intravenously - there were no studies of natalizumab administered subcutaneously. We did not identify any studies that compared subcutaneous administration of natalizumab with another intervention of interest for this appraisal. We are aware of a small number of trials that have compared different modes of administration of natalizumab, but none met inclusion criteria for our review. DELIVER[183] compared the pharmacokinetics and pharmacodynamics of single subcutaneous or intramuscular 300 mg doses of natalizumab with IV 300 mg doses in patients with MS with a short follow-up duration of 24 weeks and REFINE[184] compared switching to different dosing regimens in stable patients with RRMS who were treated with natalizumab. This study did not meet inclusion criteria for our review as all participants were already receiving natalizumab. These two studies found that natalizumab administered as a 300 mg SC injection every 4 weeks was comparable to 300 mg IV infusion natalizumab every 4 weeks in terms of ARR and CDP3 at week 60 as well as for pharmacokinetics, pharmacodynamics, and safety outcomes.

We only identified 6 trials that provided data on people with HARRMS. Two studies (MIST, and CARE-MS II) were conducted exclusively in people with HARRMS, and four reported data for a subgroup of participants with HARRMS – this included two sets of related trials that provided pooled results for the highly active subgroup. We also included the Saida 2017 trial in our synthesis of data on people with HARRMS as it was close to fulfilling our criteria of a “highly active population”. However, it should be noted that this study was restricted to Japanese patients and so results may not be generalisable to the UK population. Comparison of baseline characteristics between these populations suggested that those with highly active disease had fewer relapses as baseline, possibly as they had all been treated with DMTs in the previous year, and generally slightly worse EDSS scores. The only outcome with sufficient data to conduct an NMA for this population was ARR. To enable us to connect the network for this analysis we had to assume a class effect for interferon beta 1a (Interferon beta 1a IM30 and interferon beta 1a SC44). The findings from this analysis were very similar to the findings in the overall RRMS population. To allow direct comparison of findings between these two populations we conducted an NMA for the general RRMS population restricted to the interventions for which data were available in the HARRMS population (alemtuzumab, ocrelizumab, fingolimod, cladribine and natalizumab). Results were very similar across the two populations, although with wider credible intervals for the HARRMS population. This would be expected as there were less studies and less patients contributing to this analysis. Although we could not carry out an NMA for disease progression, we presented results for the highly active and general RRMS populations in a table to allow direct comparison between populations. This suggested that estimates were similar, with HRs generally slightly lower (i.e. suggesting a greater effect) in the highly active population, but again with wider confidence intervals. Data on adverse events and quality of

life were only reported in the CARE-MS I study and so it was difficult to draw conclusions regarding the impact of DMT on these measures in the HARRMS population.

In addition to the data from RCTs in people with HARRMS, there is some evidence from non-randomised studies on the effectiveness of natalizumab in people with HARRMS; these studies were not included in our SLR and NMA as our inclusion criteria specified that only RCTs were eligible. A recent targeted literature review and meta-analysis of natalizumab for the treatment of highly active RRMS[185] included studies in adults (≥ 18 years) with a confirmed diagnosis of RRMS who had an unchanged or increased relapse rate compared with the previous year, failed to respond to a full and adequate course of disease modifying therapy (DMT), and had experienced at least one relapse in the previous year while on therapy. They included 16 non-randomised studies that compared natalizumab to interferon beta, glatiramer acetate, teriflunomide, dimethyl fumarate and fingolimod and 11 case series of people treated with natalizumab. Data in the HARRMS population are also available for the TOP study, the largest real world study of natalizumab, that evaluated the long-term safety and efficacy of natalizumab in 6321 patients (134 UK patients) with RRMS with a follow-up pf 15 years. [154] A post-hoc subgroup analysis in a subset of patients with HARRMS, defined as those who had received prior treatment with ≥1 DMT and had experienced 1 relapse reported similar findings to the findings in the general RRMS population of a reduction of over 90% compared to the year before starting natalizumab. These findings support natalizumab improving outcomes for patients with RRMS and HARRMS, but do not provide a comparison with other interventions.

Overall, the very limited data suggest that interventions evaluated in people with HARRMS are at least as effective in this population as they are in the general RRMS population, but this should be interpreted with some caution due to the very small number of studies for which data were available in patients with HARRMS.

8.1.2 Findings on cost-effectiveness

Our systematic review of existing cost-effectiveness evaluations found seven studies for inclusion. None of these answered our decision problem of evaluating the cost-effectiveness of natalizumab and natalizumab biosimilar relative to standard of care in our target population of HARRMS after at least one disease modifying therapy. We therefore undertook an independent economic assessment.

To design the model we reviewed models used in previous relevant TAs. These were essentially the same Markov multistate model based on EDSS severity level with baseline transition rates informed by the British Columbia Multiple Sclerosis registry and London Ontario MS databases and treatment effects by individual trials and NMA. Primary criticisms of these models were that they did not capture treatment sequencing and that they were unable to accurately reflect the course of the condition. We aimed to overcome these limitations by using a DES microsimulation that allowed the modelling of treatment sequences, similar to a recent microsimulation for the Dutch RRMS guidelines. [140-143] Our model included attributes for age, sex, EDSS, SPMS status and current treatment. It modelled the events EDSS increase, EDSS decrease, progression to SPMS, relapse, SAEs, treatment discontinuation, and death. Patients could switch treatment twice, meaning that

up to 4th line therapy was included in the model. It furthermore modelled patients who progressed to SPMS with events of EDSS increase, relapse, SAEs, and death.

Event rates were a combination of natural history informed by analyses conducted by the UK MS Registry and treatment effects of ARR and CDP6 informed by the NMA. The clinical review found no evidence on AHSCT so this was not included in the economic model. Baseline SAEs and discontinuation came from AFFIRM and ANTELOPE with treatment effects from the NMA. Event rates in the SPMS population were informed purely by the MS Registry analyses as no treatment effects were assumed. Our approach to costs and utilities were aligned with previous TAs. The economic model was implemented in the R programming language using the DESCEM package.[186] The code was validated by the DESCEM develop Javier Sanchez Alvarez at Evidera.

A validation against EDSS progression over time from an earlier Markov model found that the trend predicted by the economic model was for lower increase in severity.[128] However, the earlier model was in a mixture of RRMS and SPMS and did not include the latest DMT sequences, so would be expected to have a worse prognosis. Convergence tests found the model to give stable results with greater than 100 patients and 100 samples.

Compared with natalizumab-IV, natalizumab biosimilar-IV and natalizumab-SC, all treatments had greater net benefit at £20-30,000/QALY, with the exception of ocrelizumab. The natalizumabs also had close to 0% chance of having highest net benefit at £20,000/QALY and £30,000/QALY. Costs were generally higher on natalizumab than other treatments, though there was no difference in QALYs with 95% CrI completely overlapping. Natalizumab-IV has lower mean net benefit at £20-30,000/QALY than natalizumab biosimilar-IV, although the 95% CrI overlap. Natalizumab-SC has very similar mean net benefit to Natalizumab-IV. The natalizumab biosimilar-IV has lower costs but also lower QALYs than natalizumab-IV but the 95% CrI for both are overlapping suggesting no evidence of a difference. Natalizumab-SC has very similar costs and QALYs to natalizumab-IV, again with no evidence of a difference.

We conducted sensitivity analyses testing robustness switching to All RRMS estimates from the MS Registry, switching to use of random effects NMA, using the HA RRMS NMA, excluding the price of JCV testing for branded natalizumab, reducing the natalizumab-SC treatment administration costs, using mortality stratified by EDSS severity, assuming equivalent efficacy between natalizumab and its biosimilar, using EID for natalizumab and its biosimilar, exploring alternative sources for utilities, and using an NMA with CDP3 where CDP6 is not reported. The results and conclusions were unchanged under all sensitivities. Our estimates of the EVPPI in value of information analysis found that the parameters with greatest impact on the results were the NMA treatment effects on ARR, CDP6, SAEs, and discontinuation. However, many parameters, including costs, utilities, and MS registry rates, had substantial impact on the results indicating high parameter uncertainty.

8.2 Strengths and limitations of the assessment

8.2.1 Systematic review and NMA strengths and limitations

Our systematic review followed published guidance on the conduct of systematic reviews,[46, 47] and network meta-analysis[47] and is reported according to PRISMA-2020[48] and PRISMA

guidance for NMA[49] making our review processes transparent and robust. The protocol was pre-registered on the PROSPERO database (PROSPERO 2024 CRD42024556838).[187] Changes to the protocol are clearly described in Section 4.4. Protocol changes were either to clarify issues that were ambiguous in the original protocol or to focus the review to make this manageable within the resources and time available. We clarified the inclusion criteria in relation to interventions, limiting inclusion so that only those evaluated at doses currently licensed in the UK were eligible for inclusion. This ensured that findings would be directly relevant to the UK population. Due to time and resource constraints, we focused on the following outcomes: relapse rates, proportion of participants with Gd+ and T2 weighted lesions on MRI scans, disability progression, adverse events and health-related quality of life measured using EQ-5D or SF-36. This means that we did not consider severity of relapses or symptoms of multiple sclerosis (such as fatigue , cognition, and visual disturbance) that had been specified as eligible in our protocol. These outcomes were reported inconsistently across included studies using a variety of different outcome measures and so it is unlikely that sufficient data would have been available in a consistent format to allow us to conduct an NMA for these outcome measures. Focusing on our two specific MRI measures (proportion of participants with Gd+ or new or enlarging T2 lesions) means that we were not able to considered other MRI measures such as brain lesion volume which has been proposed as a better marker of disease progression than clinical measures such as CDP6.[188]

We conducted extensive literature searches designed to maximise retrieval of relevant studies and did not apply any language, date or publication restrictions to these searches or to inclusion in the review. Four reports considered potentially relevant for inclusion and reviewed at the full text stage were reported in non-English language. We used Google Translate to assess these against our inclusion criteria and determined that none met our eligibility criteria. We pre-specified clearly defined, objective inclusion criteria. Although the population of interest for our appraisal was those with HARRMS, we defined broad inclusion criteria so that studies in any RRMS population were eligible for inclusion. We also applied a broad definition for highly active disease to include any “unchanged or increased clinical or radiological evidence of disease activity despite treatment with at least one Disease Modifying Therapy (DMT)” – this broad definition ensured that any data in a population that could be considered to have highly active disease based on definitions used in trials would be eligible for inclusion. As no data were available for natalizumab for this population, we further broadened eligibility criteria to include the Saida 2017 study that had a high proportion of patients who had been previously treated and used this as a proxy for highly active disease. This allowed us to include natalizumab in our NMA for ARR for people with HARRMS. We screened TAs that had evaluated any of the interventions or comparators of interest for this appraisal to identify additional studies and data that were relevant to the review but were not reported in publications of the trials. This allowed us to include additional data than had we only included data available in publications or clinical trial registries. We clearly report all publications and TAs related to each included study in Appendix 2, and document whether data were extracted from each report. Some of the TAs included redacted information that appeared relevant to our review but could not be included as we did not have access to this information. Data that could not be accessed that may have been informative to our review were:

- TRANSFORMS (TA254): baseline data on relapses and EDSS scores and hazard ratios for HARRMS, and EQ-5D data for general population.[40]

- CAMMS 223 (TA312): redacted QoL data – unclear what measures were reported.[39]
- OPTIMUM (TA767) – some data in HARRMS but unclear exactly what outcomes reported as full table redacted.[42]
- ASCLEPIOS I and II (TA699) – ARR, CDP3 and CDP6 for HARRMS.[41]

These data may have allowed us to include TRANSFORMS in the analysis for disease progression in the HARRMS population – this study was included for the ARR synthesis in people with HARRMS. OPTIMUM and ASCLEPIOS I & II did not report data for the HARRMS subgroup and so these data may have allowed us to include these studies for this population. However, both studies were only included to connect the network as teriflunomide was not listed as a comparator for this appraisal and so these data would only have been helpful if their inclusion created additional connected networks for the HARRMS population. In addition, the definition of HARRMS for the ASCLEPIOS studies differed from our definition as it included people previously treated with DMT who discontinued DMT due to lack of efficacy – relapses were not part of the definition. The data on QoL for TRANSFORMS and CAMMS 223 could have provided additional useful data on QoL that was rarely reported in studies included in our review.

We conducted a formal assessment of the risk of bias of included studies using the RoB 2 tool for RCTs,[55] the only tool for the assessment of risk of bias in RCTs recommended as a key tool by the LATITUDES Network.[189] Risk of bias was performed at the outcome level as recommended, the importance of following this approach was shown by the fact that for some trials risk of bias judgements differed for the different outcomes. We incorporated the risk of bias into the synthesis for ARR, the only outcome for which sufficient data were available, by conducting a sensitivity analysis restricting the analysis to studies at low risk of bias. This produced very similar results to the overall analysis suggesting that risk of bias did not impact on findings for this outcome. For all outcomes, we included the risk of bias in results tables to allow readers to qualitatively judge whether risk of bias may have impacted on study findings.

We used a new software package, Nested Knowledge, to manage the different stages of the review process. We found that this improved the efficiency of the review process and management of the review, and facilitated creation of tables for analysis and inclusion in the report. This reduced the risk of errors when exporting and manipulating data.

We employed Bayesian Network Meta-Analyses (NMA) to compare the efficacy and safety of treatment options using trial data, enabling simultaneous evaluation of multiple interventions. NMA strengthens inferences by combining direct and indirect comparisons while maintaining randomisation, making it especially useful for reviews such as our when most treatments lack head-to-head RCT comparisons. This systematic review assessed key outcomes to evaluate disease-modifying therapies (DMTs) for multiple sclerosis (MS), offering a comprehensive comparison across various domains of safety and effectiveness. Unlike previous reviews, we included studies with follow-up durations under 12 months, expanding the scope of data analysed and integrating follow-up time into calculations to account for treatment exposure. Unlike prior pooling by timepoint, all timepoints were included in a single analysis allowing us to create a more comprehensive network, as evidence from previous reviews has suggested no significant variation in rates across

timepoints. [190, 191] Additional analyses on confirmed disability progression (CDP) utilised both the CDP3 and CDP6 networks, facilitating broader comparisons between interventions. The inclusion of recently published studies ensured up-to-date data on several treatments, while analysing drugs and doses as individual nodes allowed for precise comparisons. Model selection (random- or fixed-effects) was determined based on heterogeneity and Deviance Information Criterion (DIC) values to ensure optimal fit for each analysis. Minimal heterogeneity was observed for key outcomes, including annualised relapse rate (ARR), CDP3, adverse events (AEs), and MRI outcomes, with fixed-effect models providing better data fits in these cases. The exception was CDP6 where the random effects-model provided a better fit to the data.

Our network meta-analysis (NMA) focused on interventions identified by NICE as being within the scope of this appraisal. This may have excluded some relevant treatments that are recommended for the general RRMS population but not for the HARRMS population, including dimethyl fumarate, diroximel fumarate and teriflunomide. Whilst we included studies that compared teriflunomide with interventions and comparators in scope for this appraisal, we did not expand our searches to identify studies that compared teriflunomide against other treatments such as placebo due to time and resource constraints. As teriflunomide was not identified as a comparator for this appraisal as it is not recommended for people with HARRMS, we were not aiming to provide recommendations on its effectiveness. Results for teriflunomide should therefore be interpreted with caution.

Where we calculated hazard ratios (HRs) for confirmed disability progression (CDP3 and CDP6), proportion of participants with lesions on MRI scans, and adverse events, we assumed constant HRs over time. This may not be a valid assumption, but data were not available to allow other methods of estimation. Variability across studies in definitions, follow-up times, and baseline characteristics posed challenges, though clinicians confirmed these differences were reasonably comparable. The analysis of the HARRMS population was further constrained by inconsistent definitions and data gaps for several interventions, introducing potential heterogeneity. Finally, the limited number of studies for each individual intervention restricted sensitivity analyses, potentially impacting the robustness of certain conclusions.

Many reviews have evaluated the safety and/or efficacy of treatments for MS in the past 5 years.[107, 190-200] We did not include existing reviews in our review, but we screened the included trials from recent reviews (published in past 3 years) against our review inclusion criteria to ensure that we had not missed any relevant studies. The only study included in an existing review that met our inclusion criteria but had not been included in our review was reported only in a conference abstract – we were unable to retrieve the full text of this study.[66] Most previous reviews focus only on one or two specific outcomes, for example ARR and CDP[107, 201] for adverse events,[199] or on specific interventions such as cladribine[198] or ocrelizumab.[190] The results of our review are consistent with those from other recent reviews that have included a broadly similar set of interventions, with very similar estimates of effect for ARR.[107, 201] The exception was for teriflunomide, with estimates from our review suggesting that this is less effective than found by other reviews. This may be because they differed in eligibility criteria for interventions, including all studies of teriflunomide including those compared to placebo. In contrast, we only included studies of teriflunomide to allow

us to fully include ocrelizumab in our network. Teriflunomide itself was not specified as a comparator for our review. Previous reviews[107, 190-200] have mostly focused on interventions for people with RRMS. We are only aware of one previous systematic review [202] in the HARRMS population. This review only included 2 studies comparing fingolimod and dimethyl fumarate with placebo. Our review is therefore the first to provide a comprehensive overall assessment of the effectiveness of our specified interventions and comparators in this population.

8.2.2 Limitations of the evidence base

The risk of bias (ROB) varied across studies and outcomes, with around half of studies judged at low ROB overall. No studies were classified as high ROB for the randomisation domain, although 14 studies were rated as having "some concerns" due to insufficient information on randomisation or allocation concealment but with no evidence of baseline imbalance. Five studies were at high ROB due to participants being aware of interventions and evidence of differential withdrawal across treatment groups. Another five unblinded studies showed no deviations from intended interventions and were judged at "some concerns." High ROB was observed in several trials due to a high proportion of withdrawals potentially linked to the intervention as worse outcomes could be associated with a greater likelihood of withdrawing. Six studies were rated as high ROB for missing outcome data for relapse rates with an additional eight rated high ROB for missing MRI data. There was little suggestion of missing data for adverse events, which were reported for most participants in the included trials. Although most studies used an ITT or modified ITT analysis to include all randomised participants in the analysis, few detailed the methods used for estimating outcomes for participants without follow-up data. Two studies were rated high ROB for outcome measurement due to unblinded assessors, and 14 studies had "some concerns" for selective outcome reporting, as protocols were unavailable or outcomes were inconsistently reported. We conducted a separate ROB assessment for the trials that reported data in people with highly active disease. We did not consider this to change the risk of bias for the randomisation domain, as whether or not participants had highly active disease was determined at baseline and so could not be influenced by treatment. This means that we would expect randomisation to result in equivalent groups in this sub-population.

8.2.3 Economic model strengths and limitations

We developed a novel economic model for highly active RRMS that built on the evidence and assumptions of previous NICE TAs but extended to a flexible DES approach that enabled the modelling of treatment sequences. The baseline rates of EDSS increase, EDSS decrease, relapse, and progression to SPMS were informed by a new analyses of the UK MS Registry, aligning with our target UK highly active RRMS population. Treatment effects on disability progression, relapse, adverse events and discontinuation were estimated using the high quality NMA on randomised controlled trial evidence, although it was necessary to use the all RRMS population as few trials were identified for highly active RRMS. The DES modelled disease that has progressed to SPMS, capturing the disease course beyond RRMS. A large number of treatment comparators were included, representing possible standard of care in highly active RRMS. The model was fully probabilistic with parameter uncertainty propagated from the input evidence to the final results, and considered in interpretations. Validation against published data found differences in EDSS trend over time that could be

explained by the comparator model mixing RRMS and SPMS patients and not including patients on the latest DMT sequences. Convergence tests found that results became stable with only a low number of patients and samples. Finally, value of information analysis was used instead of deterministic one-way sensitivity analysis. This considers the uncertainty in all parameters simultaneously, rather than varying parameters one at a time. Unlike deterministic sensitivity analysis, it measures a parameter as important if its uncertainty can change the decision (i.e., switch an incremental net benefit from positive to negative and vice versa) rather than only changing the net benefit or ICER themselves.

Despite the novelty and strength of evidence, the economic model also had substantial limitations. A key limitation is that treatment effects were informed by the NMA in all RRMS, rather than being based on trials in highly active RRMS. Furthermore, there was no evidence identified on autologous haematopoietic stem cell transplantation so this was not included in the economic model.

Although we used new analyses of the MS Registry to inform baseline rates of events, these were based on small sample sizes which gave uncertainty estimates. The MS Registry found no patients with highly active RRMS who decreased in EDSS so analysis could not be conducted and EDSS decrease from the all RRMS population had to be used in all analyses. It was also not possible to use the multistate modelling approach due to unstable estimates of transition rates between low EDSS states.

Our model used constant SMRs rather than varying these with EDSS states. Previous appraisals (e.g., TA767) have modelled relative risk of death being applied to each EDSS health state, taken from Pokorski (1997) but these data are considerably out of date and no replacement was identified.[42] Despite it being possible using discrete event simulation, we did not consider capacity constraints, for example with limited availability of MRI machines. Treatment stopping rates were assumed constant over time, rather than being higher in the first year of treatment than in subsequent years, which was recommended by the EAG in TA616.[38] This flexibility is possible but the NMA on discontinuation due to AE did not have sufficient data to vary rates by year since treatment initiation. The validation was limited to EDSS change over time. No suitable data were identified for a deeper validation of relapse rates and EDSS distributions.

8.3 Uncertainties

The key uncertainty remaining is whether treatment effects vary between those with RRMS and those with HA disease. There were insufficient data in people with highly active disease to fully answer this question. There was also very limited data on natalizumab biosimilar and so there is also some uncertainty in whether this is equivalent in effectiveness to natalizumab, and on whether either of these interventions is effective in those with highly active disease. This uncertainty is also key to the cost-effectiveness conclusions as the model assumed that treatment effects would not vary between those with RRMS and those with HA disease.

There were differences across studies in how outcomes, particularly relapse rates and disease progression were defined. There were insufficient data to investigate whether these differences affected estimates of treatment effect. Previous research has suggested that different ways of measuring disability may affect estimates of treatment effect.[203] There was also inconsistency in how studies defined "highly active disease". Future studies should also adopt a consistent definition.

Another key uncertainty is whether it is reasonable to assume that treatment effects remain stable over time. The economic model assumed that treatment effect were stable long-term, despite this uncertainty. For our analysis, we combined data from studies with different durations of follow-up ranging from 6 to 24 months, although most studies reported outcomes at 24 months follow-up. We had intended to conduct a sensitivity analysis to investigate whether results were different when analysed at different time points, but there were insufficient studies that reported results at 6 and 12 months follow-up for this to be possible. Three studies (AFFIRM, IFNB study and PRISMS) reported data at both 12 and 24 months follow-up. These studies reported similar estimates of ARR at the different follow-up times suggesting no difference in effect, but it was unclear whether those with 6 months follow-up would have different findings. Five studies only reported short duration of follow-up of less than 12 months (range 4 to 9 months). It may not be reasonable to expect consistency over time in MRI outcomes – our clinicians advised us that they would be less concerned about new lesions that develop within the first 6 to 12 months of treatment but would be more concerned with lesions after longer treatment duration. AEs may also differ in effects and timing depending on the specific interventions. For example, for some drugs like alemtuzumab and cladribine effects may be expected to be front loaded whereas for others a more cumulative effect may be expected. These potential differential effects were not assessed in our review and so this remains an uncertainty of our findings.

The MS Registry analyses that were used to inform the economic model had low sample size for some events. Relapse rates in the highly active RRMS were based on only 50 patients while the rate of progression to SPMS was based on only 66 patients. Furthermore, it was not possible to estimate reliable multistate transition matrix so only exponential survival models could be used for EDSS increase and decrease events.

The results themselves are highly uncertain, in particular the total and incremental QALYs. The 95% CrI are completely overlapping for all treatments, meaning that differences in effectiveness cannot be established. These are themselves due to uncertainty in the clinical evidence from the MS Registry and NMA on trials in all RRMS. However, cost differences are large and 95% CrI more rarely overlap, which leads to the observed differences in net benefit. Value of information analysis ranked the parameters on their impact on decision uncertainty, from highest to lowest, as NMA treatment effects, MS Registry baseline rates, costs, utilities, rates of discontinuation, and rates of SAEs.

8.4 Patient and Public Involvement

We involved one patient representative with lived experience of MS in this project. They attended team meetings (one at the beginning of the project and one closer to the end of the project), gave feedback on the plain language summary report, and wrote the section below about the impact that these interventions may have on people with MS.

8.5 Impact on patients

Receiving a diagnosis of highly active relapsing-remitting multiple sclerosis (RRMS) can be a challenging and emotionally taxing experience. The nature of RRMS, with its unpredictable relapses and potential for significant disability, often makes the journey to diagnosis complex and uncertain. While timely diagnosis is crucial, particularly for highly active cases, accuracy and careful tailoring of treatment plans are even more critical to ensure the best outcomes for patients. The period of waiting for a diagnosis or treatment can be overwhelming, highlighting the need for transparent communication and support throughout this process.

Advances in disease-modifying therapies (DMTs) have transformed the landscape of RRMS treatment, yet identifying the most effective and tolerable option for each individual remains a nuanced and sometimes lengthy process. Patients frequently report feeling underserved when it comes to monitoring treatment effectiveness or managing side effects. Improvements in these areas, supported by robust evidence and innovative tools, could significantly enhance care. Holistic, patient-centred approaches that prioritise early intervention, personalised treatment and psychosocial support are essential to improving quality of life for those living with RRMS.

8.6 Equality, Diversity and Inclusion

Our research was based on existing literature and so we had no control over the participants enrolled. We were broad in our inclusion criteria such that studies from any country and in any language of publication were eligible.

Our team included researchers with a broad range of experience and expertise. The lead authors are junior researchers within Bristol TAG, who were given the opportunity to lead on the writing of this report to help develop their research skills and portfolio. They were supported by the two senior authors, who provided advice and mentorship to the junior researchers leading on the reviews and health economic modelling. The team included those with expertise in systematic reviews, health economics, and medical statistics.

8.7 Implications for decision makers

There are insufficient data on natalizumab and natalizumab biosimilar in people with HARRMS. Limited evidence suggests that there is no difference in treatment effect between these interventions in people with RRMS. There is also a suggestion that other DMT have at least equivalent efficacy in people with highly active disease to that in people with RRMS. It may be reasonable to assume that this would also be the case for natalizumab and natalizumab biosimilar. The economic model made this assumption of equivalent efficacy in HARRMS as in the general RRMS and found that natalizumab and natalizumab biosimilar are

unlikely to be cost-effective. These should therefore not be recommended for people with HARRMS.

8.8 Research recommendations

There is a clear need for more studies in people with highly active disease to determine optimum treatment recommendations. There is a lack of data on the efficacy of natalizumab and natalizumab biosimilar, particularly in people with highly active disease. This was a key uncertainty in the economic model, as indicated by the value of information analysis. Further studies are needed of these interventions in people with highly active disease. Future studies should include at least 24 months follow-up to determine whether effects are sustained over a reasonable time frame. This is particularly important for assessment of disease progression, especially over longer periods of time such as CDP6. There is also a need for accepted definitions of HARRMS, relapses, and disease progression with MS. Future studies should use the same definitions to allow comparison across studies. Understanding of disease progression in HARRMS is also limited, as indicated by value of information analysis and low sample size in the MS Registry analyses. Further studies should additionally record utilities by EDSS severity and the disutilities associated of relapse and adverse events.

9 CONCLUSIONS

There were no data on the effectiveness of natalizumab or natalizumab biosimilar in patients with highly active disease. Limited data suggest that natalizumab and natalizumab biosimilar have similar effectiveness for people with RRMS population. Comparison of data on the effectiveness of DMT in people with highly active disease and those with RRMS suggest that DMTs evaluated are at least as effective in this population. However, this is based on very limited data. Assuming that natalizumab and natalizumab biosimilar follow this same pattern, it may be reasonable to assume that these interventions would also be effective in those with highly active disease. However, trials in this specific population are needed to confirm whether this is the case.

Based on the findings from the clinical review, the economic model made the assumption that treatment effects in the general RRMS population would apply to the HARRMS population and used these data and baseline rates from the MS Registry in highly active RRMS. All treatment had greater net benefit at £20-30,000/QALY than natalizumab-IV, natalizumab biosimilar-IV and natalizumab-SC, with the exception of ocrelizumab which had lower net benefits. The natalizumabs also had very low probability of having highest net benefit at £20,000/QALY and £30,000/QALY. There were no differences in costs, QALYs, or net benefit between the natalizumabs, with the 95% CrI overlapping. Analyses were robust to sensitivities and the greatest decision uncertainty was found in the treatment effects as estimated by the NMA. These findings suggests that natalizumab and natalizumab biosimilar are not cost-effective compared to standard of care in highly active RRMS but that further research is needed on the treatment effects.

10 Additional Information

10.1 Declaration of competing interests

Dr Claire Rice declares the following interests:

- Regular prescriber of Multiple Sclerosis (MS) disease modifying therapies in National Health Service (NHS) MS clinics.
- Work with the MS Society as an expert panel reviewer on grant applications.
- Research grant funded by Sanofi looking at blood biomarkers of people with MS.
- Routinely involved in clinical trials other clinical studies of people on disease modifying therapies for MS including natalizumab but these are investigator-led and are not commercial studies.

Dr Emma Tallantyre declares the following interests:

- Honorarium from Roche / Novartis for consulting work in the last 12m.
- Expenses for attending educational meetings from Merck.
- Biogen honorarium for speaker fees but not in the last 24m.

Howard Thom owns shares in Clifton Insight which has received consulting fees from Amicus, Argenx, Baxter, Bayer, Daiichi-Sankyo, Eisai, Janssen, Lundbeck, Merck, Novartis, Novo Nordisk, Pfizer, and Roche.

10.2 Contributions of authors

Catalina Lopez Manzano- Conceptualisation; data extraction and risk of bias assessment; network meta-analysis; project administration; writing – original draft; writing – reviewing and editing
Ayman Sadek- Conceptualisation; health economic modelling; project administration; visualisation; writing – original draft; writing – reviewing and editing
Chris Cooper – Literature searches and health economics review; writing – original draft
Eve Tomlinson – Data extraction; writing – reviewing and editing
Hanyu Wang – Data extraction; writing – reviewing and editing
Claire Rice - Writing – reviewing and editing; other – clinical advice
Emma Tallantyre - Writing – reviewing and editing; other – clinical advice
Ananya Rao-Middleton - Writing – reviewing and editing; other – PPI contributions
Penny Whiting – Conceptualisation; formal analysis; funding acquisition; methodology; investigation; project administration; supervision of systematic review; visualisation; writing – original draft; writing – reviewing and editing
Howard Thom - Conceptualisation; formal analysis; funding acquisition; methodology; investigation; project administration; supervision of network meta-analysis and economic modelling; visualisation; writing – original draft; writing – reviewing and editing

10.3 Acknowledgements

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10.4 Data-sharing statement

All data extracted for the systematic review and the results of the risk of bias assessments are provided in full in the appendices to this report. The economic model can be obtained from the corresponding author and will be shared upon reasonable request for academic collaboration.

10.5 Ethics Statement

The MS Registry analyses worked with primary data. This was approved by the 21/SW/0085 Southwest central Bristol ethics committee. The remainder of the research included in this report is secondary research and as such did not require ethical approval.

10.6 Information Governance Statement

There were no personal data involved in the production of this report.

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Appendix 1
Literature search strategies
Clinical effectiveness searches

Database: Ovid (MEDALL)
Host: Ovid
Data parameters: 1946 to April 130, 2024
Date of search: 1 May 2024

#	Search terms	Results
1	Multiple Sclerosis, Relapsing-Remitting/ or ((("multiple sclerosis*" or MS) and (relap* or remit*)) or RRMS).ti,ab,kf,kw.	22740
2	Natalizumab/ or (natalizumab* or antegren* or tyruko* or tysabri* or "AN-100226*" or "AN 100226*" or AN100226* or "bg-0002" or "bg 0002" or bg0002 or "dst-356a1" or "dst 356a1" or dst356a1 or "pb-006" or "pb 006" or pb006 or "pbp-2002" or "pbp 2002" or pbp2002 or L04AA23 or 3JB47N2Q2P or "189261−10−7").ti,ab,kf,kw.	3358
3	(glatiramer* or copaxobene* or copaxone* or copemyl* or copolymer* or glatect* or galtipex* or glataxon* or glatimyl* or glatopa* or glaxaton* or marcyto* or myeloxen* or perscleran* or remurel* or sclerthon* or "tv 5010" or "tv-5010" or tv5010 or "COP 1" or "COP-1" or COP1 or "Copolymer-1" or (tv adj "5010") or u782c039qp or L03AX13 or U782C039QP or "28704-27-0" or "147245−92−9").ti,ab,kf,kw.	52890
4	*INTERFERON-BETA/ or ((INTERFERON adj2 (BETA* or fibroblast)) or avonex* or extavia* or feron* or fiblaferon* or fibrolast* or frone* or hemeferon* or naferon* or "bm 532" or "bm-532" or bm532 or "SNG 001" or "SNG-001" or SNG001 or "mr 21" or "mr-21" or mr21 or V9GU1EM8SF or "74899-71-1").ti,ab,kf,kf.	15774
5	ALEMTUZUMAB/ or (alemtuzumab* or campath* or lemtrada* or mabcambath* or mabkampat* or remniq* or "bxt 1523" or "bxt-1523" or bxt1523 or "gz 402673" or "gz-402673" or gz402673 or "ldp 03" or "ldp 103" or "ldp-103" or ldp103 or L04AA34 or 3A189DH42V or "216503-57-0").ti,ab,kf,kw.	4050
6	cladribine/ or (cladribine* or biodribin* or intocel* or leustat* or leustatin* or litak* or mavenclad* or movectro* or mylinax* or "RWJ 26251" or "RWJ-26251" or RWJ26251 or L04AA40 or 47M74X9YT5 or "4291-63-8").ti,ab,kf,kw.	2634
7	Fingolimod Hydrochloride/ or (fingolimod* or bonaxon* or chantico* or efigalo* or fenoxa* or fimodigo* or fingod* or "fty 720" or "fty-720" or fty720 or gilenia* or gilenya* or golpimec* or imusera* or inzolfi* or lognif* or "ro 7079904" or "ro-7079904" or ro7079904 or tascenso* or "tdi 132" or "tdi-132" or tdi132 or L04AA27 or 3QN8BYN5QF or "162359-55-9").ti,ab,kf,kw.	4682
8	(ocrelizumab* or ocrevus* or rhumba* or "PR 070769" or "PR-070769" or PR070769 or "R 1594" or "R-1594" or R1594 or "RG 1594" or "RG-1594" or RG1594 or "RO 4964913" or "RO-4964913" or RO4964913 or L04AA36 or A10SJL62JY or "637334-45-3").ti,ab,kf,kw.	980
9	(ofatumumab* or arzerra* or kesimpta* or "HuMax CD20" or "HuMax-CD20" or HuMaxCD20 or "humac CD20" or "humac-CD20" or humacCD20 or "GSK 1841157" or "GSK-1841157" or GSK1841157 or "HSDB 8170" or "HSDB-8170" or HSDB8170 or "OMB 157" or "OMB-157" or OMB157 or L01FA02 or M95KG522R0 or "679818-59-8").ti,ab,kf,kw.	777
10	(ponesimod* or ponvory* or "ACT 128800" or "ACT-128800" or ACT128800 or "r 3477" or "r-3477" or r3477 or "rg 3477" or "rg-3477" or rg3477 or L04AA50 or 5G7AKV2MKP or "854107-55-4").ti,ab,kf,kw.	122
11	HEMATOPOIETIC STEM CELL TRANSPLANTATION/ or ((haematopoietic and stem and cell and transplant*) or (haematopoietic and stem and cell and therap*) or (hematopoietic and stem and cell and transplant*) or (hematopoietic and stem and cell and therap*) or (HSC adj1 (therap* or transplant*))).ti,ab,kf,kw.	79877
12	2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11	159934

#	Search terms	Results
13	randomized controlled trial.pt.	612247
14	controlled clinical trial.pt.	95537
15	random*.ti,ab,kf,kw.	1517590
16	placebo.ab.	247945
17	("Phase 3*" or "phase3*" or "phase III*" or P3* or "PIII*" or "Phase 2*" or "phase2*" or "phase II*" or P2* or "PII*").ti,ab,kw,kf.	407300
18	(trial or trail).ti,ab,kw,kf.	835874
19	13 or 14 or 15 or 16 or 17 or 18	2430396
20	1 and 12 and 19	2022

Database: Embase
Host: Ovid
Data parameters: 1974 to 2024 April 30
Date of search: 1 May 2024

#	Search terms	Results
1	*relapsing remitting multiple sclerosis/ or ((("multiple sclerosis*" or MS) and (relap* or remit*)) or RRMS).ti,ab,kf,kw.	45210
2	natalizumab/ or (natalizumab* or antegren* or tyruko* or tysabri* or "AN-100226*" or "AN 100226*" or AN100226* or "bg-0002" or "bg 0002" or bg0002 or "dst-356a1" or "dst 356a1" or dst356a1 or "pb-006" or "pb 006" or pb006 or "pbp-2002" or "pbp 2002" or pbp2002 or L04AA23 or 3JB47N2Q2P or "189261−10−7").ti,ab,kf,kw.	14696
3	*glatiramer/ or (glatiramer* or copaxobene* or copaxone* or copemyl* or copolymer* or glatect* or galtipex* or glataxon* or glatimyl* or glatopa* or glaxaton* or marcyto* or myeloxen* or perscleran* or remurel* or sclerthon* or "tv 5010" or "tv-5010" or tv5010 or "COP 1" or "COP-1" or COP1 or "Copolymer-1" or (tv adj "5010") or u782c039qp or L03AX13 or U782C039QP or "28704-27-0" or "147245−92−9").ti,ab,kf,kw.	55546
4	*beta interferon/ or ((INTERFERON adj2 (BETA* or fibroblast)) or avonex* or extavia* or feron* or fiblaferon* or fibrolast* or frone* or hemeferon* or naferon* or "bm 532" or "bm-532" or bm532 or "SNG 001" or "SNG-001" or SNG001 or "mr 21" or "mr-21" or mr21 or V9GU1EM8SF or "74899-71-1").ti,ab,kf,kf.	23719
5	*alemtuzumab/ or (alemtuzumab* or campath* or lemtrada* or mabcambath* or mabkampat* or remniq* or "bxt 1523" or "bxt-1523" or bxt1523 or "gz 402673" or "gz-402673" or gz402673 or "ldp 03" or "ldp 103" or "ldp-103" or ldp103 or L04AA34 or 3A189DH42V or "216503-57-0").ti,ab,kf,kw.	9493
6	*cladribine/ or (cladribine* or biodribin* or intocel* or leustat* or leustatin* or litak* or mavenclad* or movectro* or mylinax* or "RWJ 26251" or "RWJ-26251" or RWJ26251 or L04AA40 or 47M74X9YT5 or "4291-63-8").ti,ab,kf,kw.	4644
7	*fingolimod/ or (fingolimod* or bonaxon* or chantico* or efigalo* or fenoxa* or fimodigo* or fingod* or "fty 720" or "fty-720" or fty720 or gilenia* or gilenya* or golpimec* or imusera* or inzolfi* or lognif* or "ro 7079904" or "ro-7079904" or ro7079904 or tascenso* or "tdi 132" or "tdi-132" or tdi132 or L04AA27 or 3QN8BYN5QF or "162359-55-9").ti,ab,kf,kw	9012
8	*ocrelizumab/ or (ocrelizumab* or ocrevus* or rhumba* or "PR 070769" or "PR-070769" or PR070769 or "R 1594" or "R-1594" or R1594 or "RG 1594" or "RG-1594" or RG1594 or "RO 4964913" or "RO-4964913" or RO4964913 or L04AA36 or A10SJL62JY or "637334-45-3").ti,ab,kf,kw.	2587
9	*ofatumumab/ or (ofatumumab* or arzerra* or kesimpta* or "HuMax CD20" or "HuMax-CD20" or HuMaxCD20 or "humac CD20" or "humac-CD20" or humacCD20 or "GSK 1841157" or "GSK-1841157" or GSK1841157 or "HSDB 8170" or "HSDB-8170" or HSDB8170 or "OMB 157" or "OMB-157" or OMB157 or L01FA02 or M95KG522R0 or "679818-59-8").ti,ab,kf,kw.	1932

#	Search terms	Results
10	*ponesimod/ or (ponesimod* or ponvory* or "ACT 128800" or "ACT-128800" or ACT128800 or "r 3477" or "r-3477" or r3477 or "rg 3477" or "rg-3477" or rg3477 or L04AA50 or 5G7AKV2MKP or "854107-55-4").ti,ab,kf,kw.	257
11	*autologous hematopoietic stem cell transplantation/ or ((haematopoietic and stem and cell and transplant*) or (haematopoietic and stem and cell and therap*) or (hematopoietic and stem and cell and transplant*) or (hematopoietic and stem and cell and therap*) or (HSC adj1 (therap* or transplant*))).ti,ab,kf,kw.	983369
12	2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11	206490
13	randomized controlled trial/	818976
14	controlled clinical trial/	473299
15	random*.ti,ab,kf,kw.	2068701
16	placebo.ab.	366592
17	("Phase 3*" or "phase3*" or "phase III*" or P3* or "PIII*" or "Phase 2*" or "phase2*" or "phase II*" or P2* or "PII*").ti,ab,kw,kf.	638979
18	(trial or trail).ti,ab,kw,kf.	1218800
19	13 or 14 or 15 or 16 or 17 or 18	5332
20	1 and 12 and 19	2194

Clinical Trials.gov
Date of search: 8 May 2024
URL: https://classic.clinicaltrials.gov/ct2/results/refine?show_xprt=Y
Searcher location: London, UK

344 Studies found for: (Relapsing AND Remitting AND multiple sclerosis OR RRMS) AND ((natalizumab OR Tysabri OR antegren OR tyruko) OR (glatiramer OR copaxone OR brabio OR glatopa OR copolymer) OR (INTERFERON-BETA OR IFN-beta) OR (alemtuzumab OR campath OR lemtrada) OR (cladribine OR leustatin OR mavenclad) OR (fingolimod OR gilenya) OR (ocrelizumab OR ocrevus) AND OR AND (ofatumumab ORarzerra OR kesimpta OR HuMax-CD20) OR (ponesimod OR ponvory) OR autologous AND haematopoietic AND stem AND cell AND transplantation)

WHO ICTRP
Date of search: 8 May 2024
URL: https://trialsearch.who.int/Default.aspx
Searcher location: London, UK

(((Relapsing AND Remitting AND multiple sclerosis) OR (RRMS)) AND ((natalizumab OR Tysabri OR antegren OR tyruko) OR (glatiramer OR copaxone OR brabio OR glatopa OR copolymer) OR (INTERFERON-BETA OR IFN-beta) OR (alemtuzumab OR campath OR lemtrada) OR (cladribine OR leustatin OR mavenclad) OR (fingolimod OR gilenya) OR (ocrelizumab OR ocrevus) OR (ofatumumab ORarzerra OR kesimpta OR HuMax-CD20) OR (ponesimod OR ponvory) OR (autologous AND haematopoietic AND stem AND cell AND transplantation)))

Cost effectiveness and economics searches

Database: Ovid (MEDALL)
Host: Ovid
Data parameters: 1946 to May 14, 2024
Date of search: 15 May 2024

#	Search terms	Results
1	Multiple Sclerosis, Relapsing-Remitting/ or *Multiple Sclerosis, Chronic Progressive/ or (RRMS or RMS or SPMS or (("multiple sclerosis*" or MS) adj5 (relap* or remit* or secondary or progres*))).ti,ab,kf,kw.	44865
2	exp "Costs and Cost Analysis"/	270448
3	exp Economics, Hospital/ or Financial management, hospital/	33116
4	Economics, Medical/	9280
5	economics, nursing/	4013
6	economics, pharmaceutical/	3134
7	(economic* or cost or costs or costly or costing or expense or expenses or financial or price or prices or pricing or pharmacoeconomic* or "pharmaco-economic*" or CEA or CUA or CBA or CMA).ti,ab,kf,kw.	1293465
8	exp "fees and charges"/	31446
9	exp budgets/	14209
10	(resource*1 and (allocation or utili* or usage or use*1)).ti,ab,kf,kw.	289137
11	(expenditure* not energy).ti,ab,kw.	38946
12	(value adj1 (money or monetary)).ti,ab,kw.	922
13	(budget* or fiscal or funding or financial or finance*).ti,ab,kw.	252168
14	("decision tree" or Markov or "semi Markov" or "partitioned adj2 survival" or "discrete event" or "conceptual* adj2 model*" or (decision adj2 model*) or "outcome model*" or "causal model*" or (simulat* adj2 model*) or "monte carlo" or "decision tree" or QALY*).ti,ab,kf.	170283
15	2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14	1864162
16	1 and 15	2164
17	(2014* or 2015* or 2016* or 2017* or 2018* or 2019* or 2020* or 2021* or 2022* or 2023* or 2024*).dt,dp,ed,ep,yr.	14514910
18	16 and 17	1492

Database: Embase
Host: Ovid
Data parameters: 1974 to 2024 May 14
Date of search: 15 May 2024

#	Search terms	Results
1	*relapsing remitting multiple sclerosis/ or *progressive multiple sclerosis/ or (RRMS or RMS or SPMS or (("multiple sclerosis*" or MS) adj5 (relap* or remit* or secondary or progres*))).ti,ab,kf,kw.	68614
2	health-economics/	36483
3	exp economic-evaluation/	367967
4	exp health-care-cost/	352578
5	exp pharmacoeconomics/	241926
6	economics, pharmaceutical/	3134
7	(economic* or cost or costs or costly or costing or expense or expenses or financial or price or prices or pricing or pharmacoeconomic* or "pharmaco-economic*" or CEA or CUA or CBA or CMA).ti,ab,kf,kw.	1658860
8	(resource*1 and (allocation or utili* or usage or use*1)).ti,ab,kf,kw.	380346
9	(expenditure* not energy).ti,ab,kw.	52598
10	(value adj1 (money or monetary)).ti,ab,kw.	3114
11	(budget* or fiscal or funding or financial or finance*).ti,ab,kw.	372153
12	("decision tree" or Markov or "semi Markov" or "partitioned adj2 survival" or "discrete event" or "conceptual* adj2 model*" or (decision adj2 model*) or "outcome model*" or "causal model*" or (simulat* adj2 model*) or "monte carlo" or "decision tree" or QALY*).ti,ab,kf.	206543
13	2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14	2592681
14	(2014* or 2015* or 2016* or 2017* or 2018* or 2019* or 2020* or 2021* or 2022* or 2023* or 2024*).yr.	17479900
15	1 and 12 and 13	2907
16	limit 14 to embase	1229

Database: Econlit
Host: EBSCOhost
Data parameters: 1981-current
Date of search: 15 May 2024

#	Search terms	Results
1	AB (("RRMS" or "SPMS" or (("multiple sclerosis*" or MS) N5 (relap* or remit* or secondary or progres*)))) OR TI (("RRMS" or "SPMS" or (("multiple sclerosis*" or MS) N5 (relap* or remit* or secondary or progres*))))	17

Database: NHS EED (via CRD Databases)
Host: https://www.crd.york.ac.uk/CRDWeb/HomePage.asp
Data parameters: unreported
Date of search: 15 May 2024

#	Search terms	Results
1	AB (("RRMS" or "SPMS" or (("multiple sclerosis*" or MS) AND (relap* or remit* or secondary or progres*)))) OR TI (("RRMS" or "SPMS" or (("multiple sclerosis*" or MS) N5 (relap* or remit* or secondary or progres*))))	6

Appendix 2
Tables of ongoing, or excluded studies

On-going studies

Table 41 On-going studies that appear to meet inclusion criteria

Citation	Interventions of interest for this appraisal
Brittain G, Petrie J, Duffy K, et al. Efficacy and safety of autologous haematopoietic stem cell transplantation versus alemtuzumab, ocrelizumab, ofatumumab or cladribine in relapsing remitting multiple sclerosis (StarMS): protocol for a randomised controlled trial. BMJ open. 2024;14(2):e083582. doi:10.1136/bmjopen-2023-083582.	Autologous haematopoietic stem cell transplantation versus alemtuzumab, ocrelizumab, ofatumumab or cladribine
NCT03477500. *Randomized Autologous Hematopoetic Stem Cell Transplantation Versus Alemtuzumab, Cladribine or Ocrelizumab for RRMS (RAM-MS)*. URL: https://classic.clinicaltrials.gov/show/NCT03477500 (Accessed 8 May 2024).	
NCT05906992. *A Study to Compare Efficacy, Pharmacokinetics, Pharmacodynamics and Safety of CT-P53 and Ocrevus in Patients With Relapsing-remitting Multiple Sclerosis*.2023. URL: https://clinicaltrials.gov/show/NCT05906992 (Accessed 8 May 2024).	Ocrelizumab
NCT04047628. *Best Available Therapy Versus Autologous Hematopoetic Stem Cell Transplant for Multiple Sclerosis (BEAT-MS)*. URL: https://classic.clinicaltrials.gov/show/NCT04047628 (Accessed 8 May 2024).	Autologous Hematopoetic Stem Cell Transplantation
NCT04788615. *Open Label Randomized Multicenter to Assess Efficacy & Tolerability of Ofatumumab 20mg vs. First Line DMT in RMS*. URL: https://classic.clinicaltrials.gov/show/NCT04788615 (Accessed 8 May 2024).	Ofatumumab
NCT00176592. *Phase IV Study, Betaseron Versus Copaxone for Relapsing Remitting or CIS Forms of MS Using Triple Dose Gad 3 T MRI*. URL: https://classic.clinicaltrials.gov/show/NCT00176592 (Accessed 8 May 2024).	interferon beta-1b and glatiramer acetate
NCT01058005. *Study Evaluating Rebif, Copaxone, and Tysabri for Active Multiple Sclerosis*. URL: https://classic.clinicaltrials.gov/show/NCT01058005 (Accessed 8 May 2024).	interferon beta-1a and glatiramer acetate and Natilziumab
2019-001549-42. *Stem cell transplantation versus disease modifying therapy (alemtuzumab or ocrelizumab) for patients with highly active relapsing remitting MS*.2020. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2019-001549-42 (Accessed 8 May 2024).	Stem cell transplantation versus disease modifying therapy (alemtuzumab or ocrelizumab)
2010-023560-40. *Blood stem cell transplantation for patients with relapsing-remitting multiple sclerosis, in whom standard treatment has failed*.2010. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2010-023560-40 (Accessed 8 May 2024).	Stem cell transplantation versus disease modifying therapy (alemtuzumab or ocrelizumab)

Studies included in manufacturers' submissions

Below we tabulate decisions made and reasons for exclusion, where applicable, for studies reported in submissions from manfuacturers.

Table 42 Studies included in submission from BIOGEN

Study Name	Reference	Decision
AFFIRM	Polman CH, O'Connor PW, Havrdova E, *et al.* A Randomized, Placebo-Controlled Trial of Natalizumab for Relapsing Multiple Sclerosis. *N Engl J Med*. 2006;354(9):899–910. https://doi.org/10.1056/NEJMoa044397.	Included
	Hutchinson M, Kappos L, Calabresi PA, *et al.* The efficacy of natalizumab in patients with relapsing multiple sclerosis: subgroup analyses of AFFIRM and SENTINEL. *J Neurol*. 2009;256(3):405–415. https://doi.org/10.1007/s00415-009-0093-1.	Included
DELIVER	Plavina T, Fox EJ, Lucas N, Muralidharan KK, Mikol D. A Randomized Trial Evaluating Various Administration Routes of Natalizumab in Multiple Sclerosis. *J Clin Pharmacol*. 2016;56(10):1254–1262. https://doi.org/10.1002/jcph.707.	Excluded - Comparison of different administration routes
NOVA	Foley JF, Defer G, Ryerson LZ, *et al.* Comparison of switching to 6-week dosing of natalizumab versus continuing with 4-week dosing in patients with relapsing-remitting multiple sclerosis (NOVA): a randomised, controlled, open-label, phase 3b trial. *Lancet Neurol*. 2022;21(7):608–619. https://doi.org/10.1016/S1474-4422(22)00143-0.	Excluded - Comparison of different dosing schedules
REFINE	Trojano M, Ramió-Torrentà L, Grimaldi LM, *et al.* A randomized study of natalizumab dosing regimens for relapsing-remitting multiple sclerosis. *Mult Scler Houndmills Basingstoke Engl*. 2021;27(14):2240–2253.	Excluded - Comparison of different doses
TOP	Trojano M, Wiendl H, Kappos L, *et al.* TYSABRI Observational Program: Long-term Safety and Effectiveness in Relapsing-Remitting Multiple Sclerosis over 15 Years. EPO-658. Presented at European Academy of Neurology 9th Congress, 1-4 July. 2023.	Excluded - Observational Study
	Nicholas R, Harrower T, Sun Z, Davies H. Long-term Effectiveness of Natalizumab for RRMS: UK and Global 2022 Results from TYSABRI Observational Program. P184. Presented at Association of British Neurologists. 9-12 May. 2023.	

Table 43 Studies included in submission from Sandoz

Study name	Study Details	Decision
AFFIRM	Polman CH, O'Connor PW, Havrdova E, et al. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. N Engl J Med 2006;354:899-910.	Included
ANTELOPE	Hemmer B, Wiendl H, Roth K, et al. Efficacy and Safety of Proposed Biosimilar Natalizumab (PB006) in Patients With Relapsing-Remitting Multiple Sclerosis: The Antelope Phase 3 Randomized Clinical Trial. JAMA Neurol 2023;80:298-307.	Included
DELIVER	Plavina T, Fox EJ, Lucas N, et al. A Randomized Trial Evaluating Various Administration Routes of Natalizumab in Multiple Sclerosis. J Clin Pharmacol 2016;56:1254-62.	Excluded – not informative to the network: compares different protocols [Report excluded in Nested but no reason was given]
NEXT-MS	Toorop AA, van Kempen ZLE, Steenhuis M, et al. Decrease of natalizumab drug levels after switching from intravenous to subcutaneous administration in patients with multiple sclerosis. J Neurol Neurosurg Psychiatry 2023;94:482-486.	Excluded – not an RCT
REFINE	Trojano M, Ramió-Torrentà L, Grimaldi LM, et al. A randomized study of natalizumab dosing regimens for relapsing-remitting multiple sclerosis. Mult Scler 2021;27:2240-2253.	Excluded - Comparison of different doses
	ClinicalTrials.gov. Exploratory Study of the Safety, Tolerability and Efficacy of Multiple Regimens of Natalizumab in Adult Participants With Relapsing Multiple Sclerosis (MS) (REFINE). Available from: https://classic.clinicaltrials.gov/ct2/show/NCT01405820. [Last Accessed: 13th February 2024].	
TOP	Butzkueven H, Kappos L, Wiendl H, et al. Long-term safety and effectiveness of natalizumab treatment in clinical practice: 10 years of real-world data from the Tysabri Observational Program (TOP). Journal of Neurology, Neurosurgery & Psychiatry 2020;91:660-668.	Excluded - Observational Study
	Butzkueven H, Kappos L, Spelman T, et al. No evidence for loss of natalizumab effectiveness with every-6-week dosing: a propensity score-matched comparison with every-4-week dosing in patients enrolled in the Tysabri Observational Program (TOP). Ther Adv Neurol Disord 2021;14:17562864211042458.	
NR	Samjoo IA, Drudge C, Walsh S, et al. Comparative efficacy of therapies for relapsing multiple sclerosis: a systematic review and network meta-analysis. J Comp Eff Res 2023;12:e230016.	Excluded – Review (references screened)
NR	Filippi M, Danesi R, Derfuss T, et al. Early and unrestricted access to high-efficacy disease-modifying therapies: a consensus to optimize benefits for people living with multiple sclerosis. J Neurol 2022;269:1670-1677.	Excluded – Commentary
NR	Pfeuffer S, Ruck T, Pul R, et al. Impact of previous disease-modifying treatment on effectiveness and safety outcomes, among patients with multiple sclerosis treated with alemtuzumab. J Neurol Neurosurg Psychiatry 2021;92:1007-1013.	Excluded - Observational Study
NR	Killestein J, van Oosten B. Emerging safety issues in alemtuzumab-treated MS patients. Multiple Sclerosis Journal 2019;25:1206-1208.	Excluded - Editorial
NR	ClinicalTrials.gov. Safety Study of Natalizumab to Treat Multiple Sclerosis (MS). Available from: https://classic.clinicaltrials.gov/ct2/show/NCT00559702. [Last Accessed: 13th February 2024].	Excluded – Not informative to the network – compares different protocols

Study name	Study Details	Decision
NR	ClinicalTrials.gov. A Study to Evaluate Efficacy, Safety, Pharmacokinetics, and Pharmacodynamics of Multiple Doses of Natalizumab (BG00002) Administered Subcutaneously to Japanese Participants With Relapsing-Remitting Multiple Sclerosis. Available from: https://classic.clinicaltrials.gov/ct2/show/NCT05265728. [Last Accessed: 12th February 2024].	Excluded – Not an RCT
NR	ClinicalTrials.gov. A Study to Investigate the Radiological Onset of Action After Treatment Initiation With Subcutaneous (SC) Natalizumab in Participants With Relapsing-Remitting Multiple Sclerosis (RRMS). Available from: https://classic.clinicaltrials.gov/ct2/show/NCT05532163. [Last Accessed: 12th Februrary 2024].	Excluded – Not an RCT (& terminated)
NR	Gelissen LMY, Loveless S, Toorop AA, et al. Subcutaneous administration of natalizumab can lead to lower drug concentrations compared to intravenous administration. Mult Scler Relat Disord 2024;90:105796.	Excluded – Not an RCT
NR	Pelle J, Briant AR, Branger P, et al. Real-World Effectiveness of Natalizumab Extended Interval Dosing in a French Cohort. Neurol Ther 2023;12:529-542.	Excluded – Observational study
NR	Perncezky J, Sellner J. Natalizumab extended-interval dosing in multiple sclerosis to mitigate progressive multifocal leukoencephalopathy risk: initial study evidence and real-world experience. J Cent Nerv Syst Dis 2022;14:11795735221135485.	Excluded – Review
NR	Achtnichts L, Zecca C, Findling O, et al. Correlation of disability with quality of life in patients with multiple sclerosis treated with natalizumab: primary results and post hoc analysis of the TYSabri ImPROvement study (PROTYS). BMJ Neurol Open. 2023;5(1):e000304.	Excluded – Observational study

Studies excluded at full-text screening

Table 44 Reports excluded at full-text screening

Citation	Reason for exclusion
Abbasi Kasbi N, Ghadiri F, Sahraian M, et al. Comparing infusion-related reactions of the first full dose (600 mg) biosimilar ocrelizumab administration with the standard divided protocol in multiple sclerosis patients: a randomized controlled trial study. Acta neurologica Belgica. 2024;124(1):205-212. doi:10.1007/s13760-023-02366-z.	MS but not >90% RRMS
Abdar M, Ebrahimifar P, Etemadifar M. The outbreak fingolimod cardiovascular side effects in relapsing-remitting multiple sclerosis patient: A longitudinal study in an Iranian population. ARYA atherosclerosis. 2016;12(6):274-280.	Does not report on one of the outcomes of interest
Abdelgaied M, Rashad M, El-Tayebi H, Solayman M. Correction to: The impact of metformin use on the outcomes of relapse-remitting multiple sclerosis patients receiving interferon beta 1a: an exploratory prospective phase II open-label randomized controlled trial. Journal of neurology. 2024;271(5):2925. doi:10.1007/s00415-024-12249-9.	Not informative to the network - non DMT add on
Abdelgaied M, Rashad M, El-Tayebi H, Solayman M. The impact of metformin use on the outcomes of relapse-remitting multiple sclerosis patients receiving interferon beta 1a: an exploratory prospective phase II open-label randomized controlled trial. Journal of neurology. 2024;271(3):1124-1132. doi:10.1007/s00415-023-12113-2.	Not informative to the network - non DMT add on
Abramowicz M. Glatiramer acetate for relapsing multiple sclerosis. Medical Letter on Drugs and Therapeutics. 1997;39(1004):61-64.	Not a primary study
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Citation	Reason for exclusion
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Citation	Reason for exclusion
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Citation	Reason for exclusion
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Citation	Reason for exclusion
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Cascione M, Wynn D, Barbato L, Pestreich L, Schofield L, McCague K. Randomized, open-label study to evaluate patient-reported outcomes with fingolimod after changing from prior disease-modifying therapy for relapsing multiple sclerosis: EPOC study rationale and design. Journal of medical economics. 2013;16(7):859-65. doi:10.3111/13696998.2013.802239.	Not informative to the network - compares against switch to chosen iDMT
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Citation	Reason for exclusion
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Citation	Reason for exclusion
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Citation	Reason for exclusion
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Citation	Reason for exclusion
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Citation	Reason for exclusion
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Freedman M. Evidence of interferon beta-1a dose response in relapsing-remitting MS: The OWIMS study. Neurology. 1999;53(4):679-686. doi:10.1212/wnl.53.4.679.	Did not evaluate intervention of interest - drug is of interest but in different presentation/dose than licensed

Citation	Reason for exclusion
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Citation	Reason for exclusion
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Irct20120215009014N. Effect of probiotic and zinc supplementation separately and in combination on reducing the complication of influenza-like syndrome during therapy by beta-interferon in patients with relapsing-remitting multiple sclerosis.2021. URL: http://en.irct.ir/trial/53804 (Accessed 8 May 2024).	Not informative to the network - non DMT add on
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Citation	Reason for exclusion
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Citation	Reason for exclusion
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Citation	Reason for exclusion
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Kappos L, Wiendl H, Selmaj K, et al. Daclizumab HYP versus Interferon Beta-1a in Relapsing Multiple Sclerosis. The New England journal of medicine. 2015;373(15):1418-28. doi:10.1056/nejmoa1501481.	Comparator not informative to the network
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Kira J, Itoyama Y, Kikuchi S, et al. Fingolimod (FTY720) therapy in Japanese patients with relapsing multiple sclerosis over 12 months: results of a phase 2 observational extension. BMC neurology. 2014;14:21. doi:10.1186/1471-2377-14-21.	Extension/expansion study
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Knobler R, Greenstein J, Johnson K, et al. Systemic recombinant human interferon-beta treatment of relapsing-remitting multiple sclerosis: pilot study analysis and six-year follow-up. Journal of interferon research. 1993;13(5):333-40. doi:10.1089/jir.1993.13.333.	Did not evaluate intervention of interest
Koch M, Mostert J, Uitdehaag B, Cutter G. Clinical outcome measures in SPMS trials: An analysis of the IMPACT and ASCEND original trial data sets. Multiple Sclerosis Journal. 2020;26(12):1540-1549. doi:10.1177/1352458519876701.	MS but not >90% RRMS
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Citation	Reason for exclusion
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La Mantia L, Munari L, Lovati R. Glatiramer acetate for multiple sclerosis. The Cochrane database of systematic reviews. 2010;(5):CD004678. doi:10.1002/14651858.cd004678.pub2.	Review
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Lanzillo R, Quarantelli M, Pozzilli C, et al. No evidence for an effect on brain atrophy rate of atorvastatin add-on to interferon beta1b therapy in relapsing-remitting multiple sclerosis (the ARIANNA study). Multiple sclerosis (Houndmills, Basingstoke, England). 2016;22(9):1163-73. doi:10.1177/1352458515611222.	Not informative to the network - non DMT add on
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Li D, Paty D, Koopmans R, Zhao G. The effects of interferon beta-1b in multiple sclerosis as assessed by MRI. Clinical Immunotherapeutics. 1996;5(SUPPL. 1):47-54.	Did not evaluate intervention of interest
Li D, Zhao G, Paty D. Randomized controlled trial of interferon-beta-1a in secondary progressive MS: MRI results. Neurology. 2001;56(11):1505-13. doi:10.1212/wnl.56.11.1505.	MS but not >90% RRMS
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Liu Y, Vollmer T, Havrdova E, et al. Impact of daclizumab versus interferon beta-1a on patient-reported outcomes in relapsing-remitting multiple sclerosis. Multiple sclerosis and related disorders. 2017;11:18-24. doi:10.1016/j.msard.2016.11.005.	Comparator not informative to the network

Citation	Reason for exclusion
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Mancardi G, Sormani M, Gualandi F, et al. Autologous hematopoietic stem cell transplantation in multiple sclerosis: a phase II trial. Neurology. 2015;84(10):981-8. doi:10.1212/wnl.0000000000001329.	MS but not >90% RRMS
2018-000284-93. A multinational, multicenter, randomized, Phase III, double blind, parallel group, placebo controlled study in subjects with Relapsing forms of Multiple Sclerosis (RMS) to assess the efficacy, safety and tolerability of GA Depot, a long acting IM injection of glatiramer acetate, administered once every four weeks.2019. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2018-000284-93 (Accessed 8 May 2024).	Not informative to the network - drug of interest but not in a licensed dose
Irct20170604034325N. Effects of fingolimod in treatment of multiple sclerosis.2018. URL: http://en.irct.ir/trial/33624 (Accessed 8 May 2024).	Not a RCT
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Citation	Reason for exclusion
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NCT02064816. A Study of Rebif® in Subjects With Relapsing Multiple Sclerosis. URL: https://classic.clinicaltrials.gov/show/NCT02064816 (Accessed 8 May 2024).	Not informative to the network - compares different protocols
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Citation	Reason for exclusion
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NCT05123703. A Study To Evaluate Safety And Efficacy Of Ocrelizumab In Comparison With Fingolimod In Children And Adolescents With Relapsing-Remitting Multiple Sclerosis. URL: https://classic.clinicaltrials.gov/show/NCT05123703 (Accessed 8 May 2024).	RRMS but not in adults
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NCT00883337. A Study Comparing the Effectiveness and Safety of Teriflunomide and Interferon Beta-1a in Patients With Relapsing Multiple Sclerosis. URL: https://classic.clinicaltrials.gov/show/NCT00883337 (Accessed 8 May 2024).	Comparator not informative to the network
NCT01395316. Alemtuzumab on Surrogate Markers of Disease Activity and Repair Using Advanced MRI Measures in Subjects With Relapsing Remitting Multiple Sclerosis. URL: https://classic.clinicaltrials.gov/show/NCT01395316 (Accessed 8 May 2024).	Not a RCT
NCT00206648. An Efficacy and Safety Comparison Study of Two Marketed Drugs in Patients With Relapsing-remitting MS. URL: https://classic.clinicaltrials.gov/show/NCT00206648 (Accessed 8 May 2024).	Did not evaluate intervention of interest
NCT01578785. An Efficacy, Safety and Tolerability Study of Glatiramer Acetate (GA) 20 mg/0.5 ml New Formulation Administered Daily by Subcutaneous (SC) Injection in Subjects With Relapsing-Remitting Multiple Sclerosis (RRMS). URL: https://classic.clinicaltrials.gov/show/NCT01578785 (Accessed 8 May 2024).	Terminated study
NCT00930553. An Extension Protocol for Multiple Sclerosis Patients Who Participated in Genzyme-Sponsored Studies of Alemtuzumab. URL: https://classic.clinicaltrials.gov/show/NCT00930553 (Accessed 8 May 2024).	Extension/expansion study
NCT06228781. Autologous Hematopoietic Stem Cell Transplantation for Refractory Multiple Sclerosis. URL: https://classic.clinicaltrials.gov/show/NCT06228781 (Accessed 8 May 2024).	Not a RCT
NCT00168766. Avonex (Interferon-beta-1a) and Avonex Plus Methylprednisolone for the Treatment of Relapsing-remitting MS. URL: https://classic.clinicaltrials.gov/show/NCT00168766 (Accessed 8 May 2024).	Did not evaluate intervention of interest

Citation	Reason for exclusion
NCT00459667. BEYOND Follow-up: Betaferon®/Betaseron® Efficacy Yielding Outcomes of a New Dose. URL: https://classic.clinicaltrials.gov/show/NCT00459667 (Accessed 8 May 2024).	Did not evaluate intervention of interest - drug is of interest but in different presentation/dose than licensed
NCT00893217. BEYOND Pilot Study. URL: https://classic.clinicaltrials.gov/show/NCT00893217 (Accessed 8 May 2024).	Did not evaluate intervention of interest - drug is of interest but in different presentation/dose than licensed
NCT00099502. BEYOND: Betaferon/Betaseron Efficacy Yielding Outcomes of a New Dose in Multiple Sclerosis (MS) Patients. URL: https://classic.clinicaltrials.gov/show/NCT00099502 (Accessed 8 May 2024).	Did not evaluate intervention of interest
NCT01156311. BG00012 Phase 2 Combination Study in Participants With Multiple Sclerosis. URL: https://classic.clinicaltrials.gov/show/NCT01156311 (Accessed 8 May 2024).	Did not evaluate intervention of interest
NCT00605215. BRAVO Study: Laquinimod Double-blind Placebo-controlled Study in Participants With Relapsing-Remitting Multiple Sclerosis (RRMS) With a Rater Blinded Reference Arm of Interferon β-1a (Avonex®). URL: https://classic.clinicaltrials.gov/show/NCT00605215 (Accessed 8 May 2024).	Did not evaluate intervention of interest
NCT00641537. *CLARITY Extension Study*. URL: https://classic.clinicaltrials.gov/show/NCT00641537 (Accessed 8 May 2024).	Extension/expansion study
NCT01006265. Clinical Study to Evaluate the Efficacy, Safety, and Tolerability of ACT-128800 in Patients With Relapsing-remitting Multiple Sclerosis. URL: https://classic.clinicaltrials.gov/show/NCT01006265 (Accessed 8 May 2024).	Did not evaluate intervention of interest
NCT01093326. Clinical Study to Investigate the Long-term Safety, Tolerability, and Efficacy of Ponesimod in Patients With Relapsing-remitting Multiple Sclerosis. URL: https://classic.clinicaltrials.gov/show/NCT01093326 (Accessed 8 May 2024).	Did not evaluate intervention of interest
NCT00337779. Clinical Trial Comparing Treatment of Relapsing-Remitting Multiple Sclerosis (RR-MS) With Two Doses of Glatiramer Acetate (GA). URL: https://classic.clinicaltrials.gov/show/NCT00337779 (Accessed 8 May 2024).	Not informative to the network - drug of interest but not in a licensed dose
NCT00211887. Combination Therapy in Patients With Relapsing-Remitting Multiple Sclerosis (MS)CombiRx. URL: https://classic.clinicaltrials.gov/show/NCT00211887 (Accessed 8 May 2024).	Did not evaluate intervention of interest - drug is of interest but in different presentation/dose than licensed
NCT00298662. Combination Therapy of Betaseron-Prograf in Multiple Sclerosis. URL: https://classic.clinicaltrials.gov/show/NCT00298662 (Accessed 8 May 2024).	Did not evaluate intervention of interest
NCT00618527. Combination Therapy Using Cellcept and Rebif in RRMS. URL: https://classic.clinicaltrials.gov/show/NCT00618527 (Accessed 8 May 2024).	Not informative to the network - non DMT add on
NCT02744222. Comparative Clinical Trial to Evaluate Efficacy, Safety and Tolerance of BCD-054 and Avonex® for Treatment of Patients With Remitting-relapsing Multiple Sclerosis. URL: https://classic.clinicaltrials.gov/show/NCT02744222 (Accessed 8 May 2024).	Did not evaluate intervention of interest

Citation	Reason for exclusion
NCT03535298. Determining the Effectiveness of early Intensive Versus Escalation Approaches for RRMS. URL: https://classic.clinicaltrials.gov/show/NCT03535298 (Accessed 8 May 2024).	Did not evaluate intervention of interest
NCT05902429. Effects of Oral Cladribine on Remyelination and Inflammation in Multiple Sclerosis Patients. URL: https://classic.clinicaltrials.gov/show/NCT05902429 (Accessed 8 May 2024).	Not a RCT
NCT02753088. Efficacy and Safety of BCD-063 and Copaxone-Teva in Patients With Relapsing-Remitting Multiple Sclerosis. URL: https://classic.clinicaltrials.gov/show/NCT02753088 (Accessed 8 May 2024).	Not informative to the network - compares brands
NCT01064401. Efficacy and Safety of BIIB019 (Daclizumab High Yield Process) Versus Interferon β 1a in Participants With Relapsing-Remitting Multiple Sclerosis. URL: https://classic.clinicaltrials.gov/show/NCT01064401 (Accessed 8 May 2024).	Did not evaluate intervention of interest
NCT02881567. Efficacy and Safety of Daclizumab in Participants With RRMS Switching From Natalizumab. URL: https://classic.clinicaltrials.gov/show/NCT02881567 (Accessed 8 May 2024).	Did not evaluate intervention of interest
NCT00333138. Efficacy and Safety of FTY720 in Patients With Relapsing Multiple Sclerosis. URL: https://classic.clinicaltrials.gov/show/NCT00333138 (Accessed 8 May 2024).	MS but not >90% RRMS
NCT05242133. Efficacy and Safety of Peginterferon Beta-1a (CinnaGen) in Participants With Relapsing Remitting Multiple Sclerosis. URL: https://classic.clinicaltrials.gov/show/NCT05242133 (Accessed 8 May 2024).	Did not evaluate intervention of interest
NCT04115488. Efficacy and Safety of the Biosimilar Natalizumab PB006 in Comparison to Tysabri®. URL: https://classic.clinicaltrials.gov/show/NCT04115488 (Accessed 8 May 2024).	Did not evaluate intervention of interest
NCT00451451. Efficacy and Safety Study of Oral BG00012 With Active Reference in Relapsing-Remitting Multiple Sclerosis. URL: https://classic.clinicaltrials.gov/show/NCT00451451 (Accessed 8 May 2024).	Did not evaluate intervention of interest
NCT01111656. Efficacy, Safety and Tolerability of Atorvastatin 40 mg in Patients With Relapsing-remitting Multiple Sclerosis Treated With Interferon-beta-1b. URL: https://classic.clinicaltrials.gov/show/NCT01111656 (Accessed 8 May 2024).	Not informative to the network - non DMT add on
NCT01963611. Efficacy, Safety, and Tolerability of Plovamer Acetate (Pathway 1). URL: https://classic.clinicaltrials.gov/show/NCT01963611 (Accessed 8 May 2024	Did not evaluate intervention of interest
NCT03177083. Evaluate Safety/Tolerability in Portuguese Participants With RRMS Transitioning From Current Therapy. URL: https://classic.clinicaltrials.gov/show/NCT03177083 (Accessed 8 May 2024).	Comparator not informative to the network
NCT01333358. Evaluating Alemtuzumab as a Treatment in Stabilizing Neurocognitive Function In Relapsing Remitting Multiple Sclerosis Patients. URL: https://classic.clinicaltrials.gov/show/NCT01333358 (Accessed 8 May 2024).	Does not report on one of the outcomes of interest
NCT02939079. Evaluating of the Effect of Fingolimod With Fish Oil on Relapsing-Remitting Multiple Sclerosis Patients. URL: https://classic.clinicaltrials.gov/show/NCT02939079 (Accessed 8 May 2024).	Not informative to the network - non DMT add on
NCT00219908. Evaluation of a New Therapeutic Strategy in Early and Active Relapsing-Remitting Multiple Sclerosis. URL: https://classic.clinicaltrials.gov/show/NCT00219908 (Accessed 8 May 2024).	Did not evaluate intervention of interest
NCT01534182. Evaluation of Patient Reported Outcomes in RRMS Patients Candidates for MS Therapy Change and Transitioned to Fingolimod 0.5 mg (EPOC). URL: https://classic.clinicaltrials.gov/show/NCT01534182 (Accessed 8 May 2024).	Extension/expansion study
NCT01623596. Evaluation of Patient Retention of Fingolimod vs. Currently Approved Disease Modifying Therapy in Patients With Relapsing Remitting Multiple Sclerosis. URL: https://classic.clinicaltrials.gov/show/NCT01623596 (Accessed 8 May 2024).	Not a RCT

Citation	Reason for exclusion
NCT01167426. Evaluation of Two Glatiramer Acetate (GA) Formulations in Relapsing-Remitting Multiple Sclerosis (RRMS) Patients. URL: https://classic.clinicaltrials.gov/show/NCT01167426 (Accessed 8 May 2024).	Not a RCT
NCT01405820. Exploratory Study of the Safety, Tolerability and Efficacy of Multiple Regimens of Natalizumab in Adult Participants With Relapsing Multiple Sclerosis (MS). URL: https://classic.clinicaltrials.gov/show/NCT01405820 (Accessed 8 May 2024).	Not informative to the network - drug of interest but not in a licensed dose
NCT01020370. Exploratory Study to Investigate the Reparative and Regenerative Potential of Alemtuzumab in Relapsing-Remitting Multiple Sclerosis Patients Participating in the CARE MS I and MS II Studies. URL: https://classic.clinicaltrials.gov/show/NCT01020370 (Accessed 8 May 2024).	Not a RCT
NCT00235989. Extension of Prior Study Evaluating Safety and Tolerability of Two Doses of Betaseron® to Treat Relapsing-remitting Multiple Sclerosis. URL: https://classic.clinicaltrials.gov/show/NCT00235989 (Accessed 8 May 2024).	Not a RCT
NCT01416155. Extension Study to Evaluate Safety and Efficacy of Natalizumab in Japanese Participants With Relapsing-Remitting Multiple Sclerosis. URL: https://classic.clinicaltrials.gov/show/NCT01416155 (Accessed 8 May 2024).	Extension/expansion study
NCT03345940. Fingolimod Versus Dimethyl-fumarate in Multiple Sclerosis. URL: https://classic.clinicaltrials.gov/show/NCT03345940 (Accessed 8 May 2024).	Comparator not informative to the network
NCT00623415. Flupirtine as Oral Treatment in Multiple Sclerosis. URL: https://classic.clinicaltrials.gov/show/NCT00623415 (Accessed 8 May 2024).	Did not evaluate intervention of interest
NCT00203021. Glatiramer Acetate (Copaxone®) Study to Follow Participants From the First Original Study for Safety and Effectiveness. URL: https://classic.clinicaltrials.gov/show/NCT00203021 (Accessed 8 May 2024).	Not a RCT
NCT01456416. Glatiramer Acetate for Multiple Sclerosis With Autoimmune Comorbidities. URL: https://classic.clinicaltrials.gov/show/NCT01456416 (Accessed 8 May 2024).	Not a RCT
NCT00939549. High Dose Cyclophosphamide Followed by Glatiramer Acetate in the Treatment of Relapsing Remitting Multiple Sclerosis. URL: https://classic.clinicaltrials.gov/show/NCT00939549 (Accessed 8 May 2024).	Not informative to the network - non DMT add on
NCT00288626. High-Dose Immunosuppression and Autologous Transplantation for Multiple Sclerosis (HALT MS) Study. URL: https://classic.clinicaltrials.gov/show/NCT00288626 (Accessed 8 May 2024).	Not informative to the network - non DMT add on
NCT00662649. Long-term Efficacy and Safety of Fingolimod (FTY720) in Patients With Relapsing-remitting Multiple Sclerosis. URL: https://classic.clinicaltrials.gov/show/NCT00662649 (Accessed 8 May 2024).	Extension/expansion study
NCT01797965. Long-Term Extension Study in Participants With Multiple Sclerosis Who Have Completed Study 205MS301 (NCT01064401) to Evaluate the Safety and Efficacy of BIIB019. URL: https://classic.clinicaltrials.gov/show/NCT01797965 (Accessed 8 May 2024).	Extension/expansion study
NCT02307838. Long-term Follow-up of Fingolimod Phase II Study Patients. URL: https://classic.clinicaltrials.gov/show/NCT02307838 (Accessed 8 May 2024).	Not a RCT
NCT03961204. Long-Term Outcomes and Durability of Effect Following Treatment With Cladribine Tablets for MS (CLASSIC-MS). URL: https://classic.clinicaltrials.gov/show/NCT03961204 (Accessed 8 May 2024).	Not a RCT
NCT01134627. Minocycline as add-on to Interferon Beta-1a IFN Beta-1a (Rebif®) in Relapsing-Remitting Multiple Sclerosis RRMS. URL: https://classic.clinicaltrials.gov/show/NCT01134627 (Accessed 8 May 2024).	Not informative to the network - non DMT add on

Citation	Reason for exclusion
NCT00097760. Natalizumab in Combination With Glatiramer Acetate (GA) in Patients With Relapsing-Remitting Multiple Sclerosis. URL: https://classic.clinicaltrials.gov/show/NCT00097760 (Accessed 8 May 2024).	Not informative to the network - DMT add on
NCT04971005. Ocrelizumab or Alemtuzumab Compared With Autologous Hematopoietic Stem Cell Transplantation in Multiple Sclerosis - a Phase-2 Randomised Controlled Trial. URL: https://classic.clinicaltrials.gov/show/NCT04971005 (Accessed 8 May 2024).	Terminated study
NCT00473213. Optimizing IFN Beta - 1B Dose. URL: https://classic.clinicaltrials.gov/show/NCT00473213 (Accessed 8 May 2024).	Not informative to the network - compares different protocols
NCT01317004. Patients With Relapse Remitting Multiple Sclerosis (RRMS): Candidates for MS Therapy Change. URL: https://classic.clinicaltrials.gov/show/NCT01317004 (Accessed 8 May 2024).	Not informative to the network - compares against switch to chosen iDMT
NCT01464905. Phase 3 Study to Evaluate Efficacy and Safety of NU100 in Patients With Relapsing Remitting Multiple Sclerosis (RRMS). URL: https://classic.clinicaltrials.gov/show/NCT01464905 (Accessed 8 May 2024).	Did not evaluate intervention of interest
NCT02255656. Phase IIIB-IV Long-Term Follow-up Study for Patients Who Participated in CAMMS03409. URL: https://classic.clinicaltrials.gov/show/NCT02255656 (Accessed 8 May 2024).	Not a RCT
NCT00202995. Randomized Study Designed to Look at Disease Progression Using 2 Currently FDA Approved Drugs for the Treatment of RRMS. URL: https://classic.clinicaltrials.gov/show/NCT00202995 (Accessed 8 May 2024).	No results found
NCT00428584. RNF and Betaseron® Tolerability Study. URL: https://classic.clinicaltrials.gov/show/NCT00428584 (Accessed 8 May 2024).	Does not report on one of the outcomes of interest
NCT05423769. Safety and Effectiveness of Generic Fingolimod (Sphingomod®, Hikma) in Patients With Relapsing-Remitting Multiple Sclerosis in Egypt. URL: https://classic.clinicaltrials.gov/show/NCT05423769 (Accessed 8 May 2024).	Not a RCT
NCT00324506. Safety and Efficacy of Cellcept and Avonex as Combination Treatment in Multiple Sclerosis. URL: https://classic.clinicaltrials.gov/show/NCT00324506 (Accessed 8 May 2024).	Not informative to the network - non DMT add on
NCT01941004. Safety and Efficacy of Fingolimod in MS Patients in China. URL: https://classic.clinicaltrials.gov/show/NCT01941004 (Accessed 8 May 2024).	Withdrawn study
NCT02142205. Safety and Efficacy of Natalizumab (BG00002, Tysabri®) in Russian Participants With Relapsing Remitting Multiple Sclerosis (RRMS). URL: https://classic.clinicaltrials.gov/show/NCT02142205 (Accessed 8 May 2024).	Not a RCT
NCT00030966. Safety and Efficacy of Natalizumab in Combination With Avonex in the Treatment of Multiple Sclerosis. URL: https://classic.clinicaltrials.gov/show/NCT00030966 (Accessed 8 May 2024).	Not informative to the network - DMT add on
NCT00203112. Safety and Efficacy Study of Copaxone Administered in Combination With Minocycline. URL: https://classic.clinicaltrials.gov/show/NCT00203112 (Accessed 8 May 2024).	Not informative to the network - non DMT add on
NCT00203099. Safety and Efficacy Study of Copaxone Administered in Combination With N-Acetylcysteine. URL: https://classic.clinicaltrials.gov/show/NCT00203099 (Accessed 8 May 2024).	Not informative to the network - non DMT add on
NCT00246324. Safety and Efficacy Study of Doxycycline in Combination With Interferon-B-1a to Treat Multiple Sclerosis. URL: https://classic.clinicaltrials.gov/show/NCT00246324 (Accessed 8 May 2024).	Not informative to the network - non DMT add on

Citation	Reason for exclusion
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NCT01874145. Safety and Tolerability of Glatiramer Acetate. URL: https://classic.clinicaltrials.gov/show/NCT01874145 (Accessed 8 May 2024).	Not informative to the network - compares different protocols
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Citation	Reason for exclusion
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Citation	Reason for exclusion
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Citation	Reason for exclusion
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Citation	Reason for exclusion
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Citation	Reason for exclusion
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Sorensen P, Mellgren S, Svenningsson A, et al. NORdic trial of oral Methylprednisolone as add-on therapy to Interferon beta-1a for treatment of relapsing-remitting Multiple Sclerosis (NORMIMS study): a randomised, placebo-controlled trial. The Lancet. Neurology. 2009;8(6):519-29. doi:10.1016/s1474-4422(09)70085-7.	Not informative to the network - non DMT add on

Citation	Reason for exclusion
Sorensen P, Sellebjerg F, Lycke J, et al. Minocycline added to subcutaneous interferon beta-1a in multiple sclerosis: randomized RECYCLINE study. European journal of neurology. 2016;23(5):861-70. doi:10.1111/ene.12953.	Not informative to the network - non DMT add on
Steingo B, Al Malik Y, Bass A, et al. Long-term efficacy and safety of alemtuzumab in patients with RRMS: 12-year follow-up of CAMMS223. Journal of neurology. 2020;267(11):3343-3353. doi:10.1007/s00415-020-09983-1.	Extension/expansion study
Stelmasiak Z, Solski J, Nowicki J, Jakubowska B, Ryba M, Grieb P. Effect of parenteral cladribine on relapse rates in patients with relapsing forms of multiple sclerosis: results of a 2-year, double-blind, placebo-controlled, crossover study. Multiple sclerosis (Houndmills, Basingstoke, England). 2009;15(6):767-70. doi:10.1177/1352458509103610.	MS but not >90% RRMS
Stepien A, Chalimoniuk M, Lubina-Dabrowska N, Chrapusta S, Galbo H, Langfort J. Effects of interferon beta-1a and interferon beta-1b monotherapies on selected serum cytokines and nitrite levels in patients with relapsing-remitting multiple sclerosis: a 3-year longitudinal study. Neuroimmunomodulation. 2013;20(4):213-22. doi:10.1159/000348701.	Not a RCT
NCT05834855. *Non-inferiority Study of Rituximab Compared to Ocrelizumab in Relapsing MS*.2023. URL: https://clinicaltrials.gov/show/NCT05834855 (Accessed 8 May 2024).	Did not evaluate intervention of interest
jRCT2031210175. *Protocol Number; COMB157G1401*.2021. URL: https://jrct.niph.go.jp/latest-detail/jRCT2031210175 (Accessed 8 May 2024).	Extension/expansion study
Svenningsson A, Frisell T, Burman J, et al. Safety and efficacy of rituximab versus dimethyl fumarate in patients with relapsing-remitting multiple sclerosis or clinically isolated syndrome in Sweden: a rater-blinded, phase 3, randomised controlled trial. The Lancet. Neurology. 2022;21(8):693-703. doi:10.1016/s1474-4422(22)00209-5.	Did not evaluate intervention of interest
2011-000888-27. *A clinical trial comparing the efficacy, and safety and tolerability of two disease modifying MS drugs (GTR and Copaxone®) in patients with relapsing remitting multiple sclerosis for 9 months followed by a 15 month GTR treatment part to evaluate efficacy and safety of long-term GTR treatment*.2011. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2011-000888-27 (Accessed 8 May 2024).	Not informative to the network - compares brands
2013-002082-19. *A clinical study in subjects with relapsing-remitting multiple sclerosis (RRMS) to assess the efficacy, safety and tolerability of two oral doses of laquinimod either of 0.6 mg/day or 1.2mg/day (experimental drug) as compared to Interferon ß-1a (Avonex, authorised drug) administered once weekly*.2013. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2013-002082-19 (Accessed 8 May 2024).	Comparator not informative to the network
2006-002037-20. *A multi-national, multi-centre, randomized, parallel-group, double-blind study to compare the efficacy, tolerability and safety of Glatiramer Acetate Injection 40 mg/ml to that of Glatiramer Acetate Injection 20 mg/ml administered once daily by subcutaneous injection in subjects with relapsing remitting (RR) Multiple Sclerosis (MS) - FORTE*.2006. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2006-002037-20 (Accessed 8 May 2024).	Not informative to the network - compares different protocols
2011-005550-57. *A clinical study in patients with multiple sclerosis to assess the efficacy, safety and tolerability of Glatiramer Acetate (GA) 20 mg/0.5 ml (experimental drug)*.2012. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2011-005550-57 (Accessed 8 May 2024).	Terminated study
Togha M, Karvigh S, Nabavi M, et al. Simvastatin treatment in patients with relapsing-remitting multiple sclerosis receiving interferon beta 1a: a double-blind randomized controlled trial. Multiple sclerosis (Houndmills, Basingstoke, England). 2010;16(7):848-54. doi:10.1177/1352458510369147.	Not informative to the network - non DMT add on

Citation	Reason for exclusion
Toghianifar N, Ashtari F, Zarkesh-Esfahani S, Mansourian M. Effect of high dose vitamin D intake on interleukin-17 levels in multiple sclerosis: a randomized, double-blind, placebo-controlled clinical trial. Journal of neuroimmunology. 2015;285:125-8. doi:10.1016/j.jneuroim.2015.05.022.	Not informative to the network - non DMT add on
Toorop A, van Lierop Z, Gelissen L, et al. Prospective trial of natalizumab personalised extended interval dosing by therapeutic drug monitoring in relapsing-remitting multiple sclerosis (NEXT-MS). Journal of neurology, neurosurgery, and psychiatry. 2024;95(5):392-400. doi:10.1136/jnnp-2023-332119.	Not a primary study
Tremlett H. Randomized multicenter trial of natalizumab in acute MS relapses: clinical and MRI effects. Neurology. 2005;64(1):174-5. doi:10.1212/wnl.64.1.174.	Not a primary study
Trojano M, Ramio-Torrenta L, Grimaldi L, et al. A randomized study of natalizumab dosing regimens for relapsing-remitting multiple sclerosis. Multiple sclerosis (Houndmills, Basingstoke, England). 2021;27(14):2240-2253. doi:10.1177/13524585211003020.	Did not evaluate intervention of interest
2006-004937-13. *multicentee randomized controlled study of azathioprine versus iterferon beta in relapsing remitting multiple sclerosis - M.A.I.N. trial*.2007. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2006-004937-13 (Accessed 8 May 2024).	Not a primary study
2017-005129-18. *Clinical trial to evaluate the effectiveness and safety of IFN beta-1a (IFN beta-1a), injected once a week via intramuscolar (i.m.), and glatiramer-acetate (GA) in children/adolescent patients with multiple sclerosis*.2018. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2017-005129-18 (Accessed 8 May 2024).	RRMS but not in adults
2014-000709-10. *Investigation on how alemtuzumab acts in patients with relapsing remitting multiple sclerosis*.2014. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2014-000709-10 (Accessed 8 May 2024).	Not a RCT
NCT04578639. *Ocrelizumab VErsus Rituximab Off-Label at the Onset of Relapsing MS Disease*.2020. URL: https://clinicaltrials.gov/ct2/show/NCT04578639 (Accessed 8 May 2024).	Did not evaluate intervention of interest
2016-001166-29. *A randomised controlled trial to compare ocrelizumab or alemtuzumab with autologous hematopoietic stem cell transplantation (aHSCT) in high inflammatory multiple sclerosis (COAST)*.2019. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2016-001166-29 (Accessed 8 May 2024).	Terminated study
2013-002378-26. *Switch To RItuXimab in MS extension An extension study of an ongoing clinical trial where people with multiple sclerosis switch therapy from interferon or glatiramere injections to rituximab, a monoclonal antibody that eliminate B lymphocytes*.2013. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2013-002378-26 (Accessed 8 May 2024).	Did not evaluate intervention of interest
Valenzuela B, Olsson Gisleskog P, Poggesi I, et al. An exposure-response analysis of ponesimod clinical efficacy in a randomized phase III study in patients with relapsing multiple sclerosis. CPT: pharmacometrics & systems pharmacology. 2022;11(10):1294-1304. doi:10.1002/psp4.12778.	Does not report on one of the outcomes of interest
Van Wijmeersch B, Singer B, Boster A, et al. Efficacy of alemtuzumab over 6 years in relapsing-remitting multiple sclerosis patients who relapsed between courses 1 and 2: Post hoc analysis of the CARE-MS studies. Multiple Sclerosis Journal. 2020;26(13):1719-1728. doi:10.1177/1352458519881759.	Extension/expansion study

Citation	Reason for exclusion
Vermersch P, Czlonkowska A, Grimaldi L, et al. Teriflunomide versus subcutaneous interferon beta-1a in patients with relapsing multiple sclerosis: a randomised, controlled phase 3 trial. Multiple sclerosis (Houndmills, Basingstoke, England). 2014;20(6):705-16. doi:10.1177/1352458513507821.	Comparator not informative to the network
Vermersch P, Scaramozza M, Levin S, et al. Effect of Dimethyl Fumarate vs Interferon beta-1a in Patients With Pediatric-Onset Multiple Sclerosis: The CONNECT Randomized Clinical Trial. JAMA network open. 2022;5(9):e2230439. doi:10.1001/jamanetworkopen.2022.30439.	MS but not >90% RRMS
Irct201705108323N. *Evaluating the efficacy and side effects fingolimod in 3 -year follow-up of patients with recurrent forms of multiple sclerosis*.2017. URL: http://en.irct.ir/trial/8804 (Accessed 8 May 2024).	Not a RCT
Irct201112267419N. *Randomized, open labeled, multicenter study evaluating safety Fingolide® in patients with Relapsing-Remitting Multiple Sclerosis*.2012. URL: http://en.irct.ir/trial/7881 (Accessed 8 May 2024).	Not a RCT
Irct201406018323N. *The evaluation of the efficacy and safety of oral fingolimod in relapsing remitting multiple sclerosis*.2015. URL: http://en.irct.ir/trial/8799 (Accessed 8 May 2024).	Not a RCT
Vollmer T, Cohen J, Alvarez E, et al. Safety results of administering ocrelizumab per a shorter infusion protocol in patients with primary progressive and relapsing multiple sclerosis. Multiple sclerosis and related disorders. 2020;46:102454. doi:10.1016/j.msard.2020.102454.	Comparator not informative to the network
Vollmer T, Panitch H, Bar-Or A, et al. Glatiramer acetate after induction therapy with mitoxantrone in relapsing multiple sclerosis. Multiple sclerosis (Houndmills, Basingstoke, England). 2008;14(5):663-70. doi:10.1177/1352458507085759.	Did not evaluate intervention of interest
Vollmer T, Sorensen P, Selmaj K, et al. A randomized placebo-controlled phase III trial of oral laquinimod for multiple sclerosis. Journal of neurology. 2014;261(4):773-83. doi:10.1007/s00415-014-7264-4.	Comparator not informative to the network
Voskuhl R, Wang H, Wu T, et al. Estriol combined with glatiramer acetate for women with relapsing-remitting multiple sclerosis: a randomised, placebo-controlled, phase 2 trial. The Lancet. Neurology. 2016;15(1):35-46. doi:10.1016/s1474-4422(15)00322-1.	Not informative to the network - non DMT add on
NCT04458688. *Investigating the Effect of Ocrelizumab in African Americans and Caucasians With Relapsing Multiple Sclerosis*.2020. URL: https://clinicaltrials.gov/show/NCT04458688 (Accessed 8 May 2024).	Not a RCT
Wolinsky J, Borresen T, Dietrich D, et al. GLACIER: An open-label, randomized, multicenter study to assess the safety and tolerability of glatiramer acetate 40 mg three-times weekly versus 20 mg daily in patients with relapsing-remitting multiple sclerosis. Multiple sclerosis and related disorders. 2015;4(4):370-6. doi:10.1016/j.msard.2015.06.005.	Did not evaluate intervention of interest
Wray S, Then Bergh F, Wundes A, et al. Efficacy and Safety Outcomes with Diroximel Fumarate After Switching from Prior Therapies or Continuing on DRF: Results from the Phase 3 EVOLVE-MS-1 Study. Advances in therapy. 2022;39(4):1810-1831. doi:10.1007/s12325-022-02068-7.	Did not evaluate intervention of interest
Wroe S. Effects of dose titration on tolerability and efficacy of interferon beta-1b in people with multiple sclerosis. The Journal of international medical research. 2005;33(3):309-18. doi:10.1177/147323000503300306.	Not informative to the network - compares different protocols
Wynn D, Kaufman M, Montalban X, et al. Daclizumab in active relapsing multiple sclerosis (CHOICE study): a phase 2, randomised, double-blind, placebo-controlled, add-on trial with interferon beta. The Lancet. Neurology. 2010;9(4):381-90. doi:10.1016/s1474-4422(10)70033-8.	Not informative to the network - non DMT add on

Citation	Reason for exclusion
Wynn D, Meyer C, Allen N, O'Brien D. Optimal dosing of immunomodulating drugs: A dose-comparison study of GA in RRMS. Progress in Neurotherapeutics and Neuropsychopharmacology. 2008;3(1):137-151. doi:10.1017/s1748232107000110.	Not informative to the network - drug of interest but not in a licensed dose
2012-003735-32. *Study to compare the efficacy and/or safety of masitinib to interferon beta-1a, interferon beta-1b, peginterferon beta-1a or glatiramer acetate in patients with relapsing remitting multiple sclerosis with unsatisfactory response to these first line treatments*.2015. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2012-003735-32 (Accessed 8 May 2024).	Terminated study
2021-005746-15. *A Rollover Study to Evaluate the Long-Term Safety and Efficacy of Ocrelizumab In Patients with Multiple Sclerosis*.2022. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2021-005746-15 (Accessed 8 May 2024).	Not a RCT
2020-004128-41. *A Study to Evaluate Safety and Efficacy of Ocrelizumab in Comparison with Fingolimod in Children and Adolescents with Relapsing-Remitting Multiple Sclerosis*.2021. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2020-004128-41 (Accessed 8 May 2024).	RRMS but not in adults
2015-005597-38. *A Study to Evaluate the Efficacy and Safety of Ocrelizumab in Patients With Relapsing Remitting Multiple Sclerosis*.2016. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2015-005597-38 (Accessed 8 May 2024).	Not an RCT
2020-000893-69. *A Study to Evaluate the Efficacy, Safety and Pharmacokinetics of a Higher Dose of Ocrelizumab in Adults with Relapsing Multiple Sclerosis*.2020. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2020-000893-69 (Accessed 8 May 2024).	Not informative to the network - compares different protocols
32113. *A Phase IIIB, Double Blind, Placebo-Controlled, Multcenter, Parallel Group, Extension Trial to Evaluate the Safety and Tolerability of Oral Cladribine in Subjects with Relapsing-Remitting Multiple Sclerosis Who Have Completed Trial 25643 (Clarity)*.2008. URL: https://onderzoekmetmensen.nl/en/trial/32113 (Accessed 8 May 2024).	Extension/expansion study
2010-024017-31. *A 6-month, Randomized, Active Comparator, Open-label, Multi-Center Study to Evaluate Patient OutComes, Safety and Tolerability of Fingolimod (FTY720) 0.5 mg/day in Patients with Relapsing Remitting Multiple Sclerosis who are candidates for MS therapy change from Previous Disease Modifying Therapy - GOLDEN*.2011. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2010-024017-31 (Accessed 8 May 2024).	Comparator not informative to the network
2014-001012-19. *Effects of fingolimod on advanced brain measures and clinical measures in multiple sclerosis*.2014. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2014-001012-19 (Accessed 8 May 2024).	Not a RCT
Zarbin M, Jampol L, Jager R, et al. Ophthalmic evaluations in clinical studies of fingolimod (FTY720) in multiple sclerosis. Ophthalmology. 2013;120(7):1432-9. doi:10.1016/j.ophtha.2012.12.040.	Extension/expansion study
Zavalishin I, Gusev E, Iakhno N, et al. [Results of a multicenter study of Rebif-22 mcg administration in Russia]. Rezul'taty multitsentrovogo issledovaniia effektivnosti preparata Rebif-22 mkg v Rossii. 2003;(Spec No 2):73-8.	Not a RCT
Zecca C, Riccitelli G, Calabrese P, et al. Treatment satisfaction, adherence and behavioral assessment in patients de-escalating from natalizumab to interferon beta. BMC neurology. 2014;14:38. doi:10.1186/1471-2377-14-38.	Did not evaluate intervention of interest

Citation	Reason for exclusion
Ziemssen T, Bass A, Berkovich R, et al. Efficacy and Safety of Alemtuzumab Through 9 Years of Follow-up in Patients with Highly Active Disease: Post Hoc Analysis of CARE-MS I and II Patients in the TOPAZ Extension Study. CNS drugs. 2020;34(9):973-988. doi:10.1007/s40263-020-00749-x.	Extension/expansion study
Zimmermann C, Walther E, Goebels N, et al. [Interferon beta-1b for treatment of secondary chronic progressive multiple sclerosis]. Interferon beta-1b zur Behandlung der sekundar chronisch progredienten multiplen Sklerose. 1999;70(8):759-63. doi:10.1007/s001150050508.	MS but not >90% RRMS

Studies excluded at full-text screening (Review of Cost-effectiveness)

Table 45 Studies excluded at full-text screening (Review of Cost-effectiveness)

Citation	Reason for exclusion
Ahmad H, Campbell JA, van der Mei I, Taylor BV, Xia Q, Zhao T, et al. Estimating the disutility of relapse in relapsing-remitting and secondary progressive multiple sclerosis using the EQ-5D-5L, AQoL-8D, EQ-5D-5L-psychosocial, and SF-6D: implications for health economic evaluation models. Quality of Life Research 2023;32(12):	Exclude not an economic evaluation
Ahmad H, van der Mei I, Taylor B, Zhao T, Xia Q, Palmer AJ. Does health-related quality of life differ between people with relapse onset and progressive onset Multiple Sclerosis? Multiple Sclerosis and Related Disorders 2021;54	Exclude QoL
Alasdair Millar J. The cost of teriflunomide in the treatment of relapsing remitting multiple sclerosis. New Zealand Medical Journal 2019;132	Exclude RRMS New Zealand
Alharbi MA, Aldosari F, Althobaiti AH, Abdullah FM, Aljarallah S, Alkhawajah NM, et al. Clinical and economic evaluations of natalizumab, rituximab, and ocrelizumab for the management of relapsing-remitting multiple sclerosis in Saudi Arabia. BMC Health Services Research 2023;23(1):	Exclude RRMS Saudia Arabia
Allen F, Montgomery S, Maruszczak M, Kusel J, Adlard N. Convergence yet Continued Complexity: A Systematic Review and Critique of Health Economic Models of Relapsing-Remitting Multiple Sclerosis in the United Kingdom. Value in Health 2015;18(6):	Exclude not an economic evaluation
Allignol A, Boutmy E, Sabido Espin M, Marhardt K, Vermersch P. Effectiveness, Healthcare Resource Utilization and Adherence to Subcutaneous Interferon Beta-1a According to Age in Patients With Multiple Sclerosis: A Cohort Study Using a US Claims Database. Frontiers in neurology [electronic resource] 2021;12	Exclude not an economic evaluation
Alping P, Neovius M, Piehl F, Frisell T. Real-World Healthcare Cost Savings and Reduced Relapse Rate with Off-Label Rituximab versus Disease-Modifying Treatments Approved for Relapsing-Remitting Multiple Sclerosis: A Nationwide Cost-Effectiveness Study. Annals of Neurology 2024;26	Exclude RRMS Sweden
Alsaqa'aby MF, Vaidya V, Khreis N, Al Khairallah T, Al-Jedai AH. Cost-effectiveness of oral agents in relapsing-remitting multiple sclerosis compared to interferon-based therapy in Saudi Arabia. Annals of Saudi Medicine 2017;37	Exclude RRMS Saudi Arabia
Alvarez Ayuso L, Rodriguez Marrodan B, Blasco Quilez MR, Garcia-Merino JA, Sanchez Guerrero A. Economic impact of the new oral treatments for multiple sclerosis. Neurologia 2021;36(2):	Exclude RRMS Spain
Araujo L, Kyatham S, Bzdek KG, Higuchi K, Greene N. Assessing the Health Economic Outcomes from Commercially Insured Relapsing Multiple Sclerosis Patients Who Switched from Other Disease-Modifying Therapies to Teriflunomide, in the United States. Clinicoeconomics & Outcomes Research 2023;15	Exclude not an economic evaluation
Armoiry X, Spath HM, Henaine AM, Dussart C, Counsell C, Connock M. Ocrelizumab not recommended in France for patients with primary progressive multiple sclerosis while recommended in England: a review comparing the assessment by HAS and NICE. Expert Opinion on Biological Therapy 2021;21(6):	Exclude not an economic evaluation
Asadollahi M, Darvishi A, Azimi A, Annabi M, Jafariazar Z, Heshmat R. Economic Burden of Multiple Sclerosis Drugs in Iran during 2011-2019. Iranian Journal of Public Health 2023;52(2):	Exclude MS Iran
Auguste P, Colquitt J, Connock M, Loveman E, Court R, Ciccarelli O, et al. Ocrelizumab for Treating Patients with Primary Progressive Multiple Sclerosis: An Evidence Review Group Perspective of a NICE Single Technology Appraisal. PharmacoEconomics 2020;38(6):	Exclude not an economic evaluation

Citation	Reason for exclusion
Aungsumart S, Apiwattanakul M. Clinical and fringe benefits of rituximab in multiple sclerosis treatment in a poor resource setting: Case series and cost analysis. *Multiple Sclerosis and Related Disorders* 2023;**73**	Exclude MS Thailand
Aungsumart S, Turongkaravee S, Youngkong S, Apiwattanakul M, Thakkinstian A, Chaikledkaew U. Rituximab for the treatment of relapsing-remitting multiple sclerosis in Thailand: an economic evaluation and budget impact analysis. *BMC Health Services Research* 2023;**23**(1):	Exclude MS Thailand
Avxentyev NA, Davydovskaya MV, Makarova YV, Frolov MY, Klabukova DL. [Pharmacoeconomic aspects of using cladribine (in tablets) for treatment of adult patients with remitting multiple sclerosis]. *Farmakoekonomicheskie aspekty primeneniya kladribina dlya lecheniya vzroslykh patsientov s vysokoaktivnym remittiruyushchim rasseyannym sklerozom* 2021;**121**(8): 30-36	Exclude RRMS Russia
Ayati N, Fleifel L, Sharifi S, Sahraian MA, Nikfar S. Cladribine tablets are a cost-effective strategy in high-disease activity relapsing multiple sclerosis patients in Iran. Current Journal of Neurology 2021;20(3):	Exclude RRMS Iran
Baharnoori M, Bhan V, Clift F, Thomas K, Mouallif S, Adlard N, et al. Cost-Effectiveness Analysis of Ofatumumab for the Treatment of Relapsing-Remitting Multiple Sclerosis in Canada. PharmacoEconomics Open 2022;6(6):	Exclude RRMS Canada
Bargiela D, Bianchi MT, Westover MB, Chibnik LB, Healy BC, De Jager PL, et al. Selection of first-line therapy in multiple sclerosis using risk-benefit decision analysis. Neurology 2017;88(7):	Exclude RRMS US
Bayen E, Papeix C, Pradat-Diehl P, Lubetzki C, Joel ME. Patterns of Objective and Subjective Burden of Informal Caregivers in Multiple Sclerosis. *Behavioural Neurology* 2015;**2015**	Exclude not an economic evaluation
Ben-Amor AF, Trochanov A, Fischer TZ. Cumulative Review of Thrombotic Microangiopathy, Thrombotic Thrombocytopenic Purpura, and Hemolytic Uremic Syndrome Reports with Subcutaneous Interferon beta-1a. *Advances in Therapy* 2015;**32**(5):	Exclude not an economic evaluation
Bergamaschi R, Agnello M, Colombo E, Della Giovanna M, Montomoli C, Nava A*, et al.* Detection of clinical relapses in multiple sclerosis cohorts: construction and validation of a model based on administrative data. *Neurological Sciences* 2014;**35**(2):	Exclude RRMS Italy
Bergvall N, Lahoz R, Reynolds T, Korn JR. Healthcare resource use and relapses with fingolimod versus natalizumab for treating multiple sclerosis: a retrospective US claims database analysis. *Current Medical Research & Opinion* 2014;**30**(8):	Exclude MS US
Bhan V, Clift F, Baharnoori M, Thomas K, Patel BP, Blanchette F*, et al.* Cost-consequence analysis of ofatumumab for the treatment of relapsing-remitting multiple sclerosis in Canada. *Journal of Comparative Effectiveness Research* 2023;**12**(9):	Exclude RRMS Canada
Blackney M, Kelly M, Zeidman R, Andreykiv M, Plich A. The Cost Burden of Switching Patients with Relapsing-Remitting Multiple Sclerosis from Glatiramer Acetate To Newly-Approved Disease Modifying Therapies. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research* 2014;**17**(7): A393	Exclude abstract only
Bogosian A, Chadwick P, Windgassen S, Norton S, McCrone P, Mosweu I*, et al.* Distress improves after mindfulness training for progressive MS: A pilot randomised trial. *Multiple Sclerosis* 2015;**21**(9):	Exclude not an economic evaluation
Bohlega S, Elboghdady A, Al-Johani A, Mahajan K, Mughari MK, Al-Saqa'aby M*, et al.* Economic Evaluation of Cladribine Tablets in Patients With High Disease Activity-Relapsing-Remitting Multiple Sclerosis in the Kingdom of Saudi Arabia. *Value in Health Regional Issues* 2021;**25**	Exclude RRMS Saudi Arabia
Bowen JD, Kozma CM, Grosso MM, Phillips AL. A real-world comparison of relapse rates, healthcare costs and resource use among patients with multiple sclerosis newly initiating subcutaneous interferon beta-1a versus oral disease-modifying drugs. *Multiple Sclerosis Journal Experimental Translational & Clinical* 2018;**4**(4):	Exclude MS US
Bozkaya D, Livingston T, Migliaccio-Walle K, Odom T. The cost-effectiveness of disease-modifying therapies for the treatment of relapsing-remitting multiple sclerosis. *Journal of Medical Economics* 2017;**20**(3):	Exclude RRMS US

Citation	Reason for exclusion
Brown LJ, Li J, Brunner M, Snoke M, La HA. Societal costs of primary progressive multiple sclerosis in Australia and the economic impact of a hypothetical disease-modifying treatment that could delay disease progression. *Journal of Medical Economics* 2021;**24**(1):	Exclude PPMS Australia
Bruno D, Marc D, Ouarda P, Dominique S, Marc S, Laurene C*, et al.* Economic burden of multiple sclerosis in France estimated from a regional medical registry and national sick fund claims. *Multiple Sclerosis and Related Disorders* 2019;**36**	Exclude MS France
Burks J, Marshall TS, Ye X. Adherence to disease-modifying therapies and its impact on relapse, health resource utilization, and costs among patients with multiple sclerosis. *Clinicoeconomics & Outcomes Research* 2017;**9**	Exclude MS US
Burt RK, Tappenden P, Han X, Quigley K, Arnautovic I, Sharrack B*, et al.* Health economics and patient outcomes of hematopoietic stem cell transplantation versus disease-modifying therapies for relapsing remitting multiple sclerosis in the United States of America. *Multiple Sclerosis and Related Disorders* 2020;**45**	Exclude RRMS US
Cabreira V, Abreu P, Maia C, Costa A, Sa MJ. Trends in hospital readmissions in Multiple Sclerosis patients between 2009 and 2015. *Multiple Sclerosis and Related Disorders* 2020;**45**	Exclude not an economic evaluation
CADTH drug review of Ofatumumab (Kesimpta) submitted by Novartis	Exclude RRMS Canada
Calocer F, Dejardin O, Droulon K, Launoy G, Defer G. Socio-economic status influences access to second-line disease modifying treatment in Relapsing Remitting Multiple Sclerosis patients. *PLoS ONE [Electronic Resource]* 2018;**13**(2):	Exclude RRMS France
Capkun G, Lahoz R, Verdun E, Song X, Chen W, Korn JR*, et al.* Expanding the use of administrative claims databases in conducting clinical real-world evidence studies in multiple sclerosis. *Current Medical Research & Opinion* 2015;**31**(5):	Exclude not an economic evaluation
Casado V, Bonaventura I, Brieva L, Martinez-Yelamos S, Martin G, Presas-Rodriguez S*, et al. Neurology Perspectives* 2021;**1**	Exclude RRMS Spain
Centonze D, Iannazzo S, Santoni L, Saleri C, Puma E, Giuliani L*, et al.* The economic profile of peginterferon beta-1a in the treatment of relapsing-remitting multiple sclerosis in Italy. *Multiple Sclerosis and Demyelinating Disorders* 2017;**2**	Exclude RRMS Italy
Chalkou K, Steyerberg E, Bossuyt P, Subramaniam S, Benkert P, Kuhle J*, et al.* Development, validation and clinical usefulness of a prognostic model for relapse in relapsing-remitting multiple sclerosis. *Diagnostic and Prognostic Research* 2021;**5**(1):	Exclude RRMS Swiss
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Nagpal A, Milte R, Kim SW, Hillier S, Hamilton-Bruce MA, Ratcliffe J*, et al.* Economic Evaluation of Stem Cell Therapies in Neurological Diseases: A Systematic Review. *Value in Health* 2019;**22**(2):	Exclude SPMS
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Navarro CE, Betancur JE. Cost-Utility Analysis Comparing Ocrelizumab Versus Rituximab in the Treatment of Relapsing-Remitting Multiple Sclerosis: The Colombian Perspective. *Value in Health Regional Issues* 2023;**36**	Exclude RRMS Colombia
Navarro CE, Ordonez-Callamand E, Alzate JP. Disease modifying therapies in multiple sclerosis: cost-effectiveness systematic review. *Farmacia Hospitalaria* 2020;**44**(2):	Exclude RRMS Colombia
Nazareth T, Datar M, Yu TC. Treatment Effectiveness for Resolution of Multiple Sclerosis Relapse in a US Health Plan Population. *Neurology & Therapy* 2019;**8**(2):	Exclude MS US
Ness NH, Schriefer D, Haase R, Ettle B, Cornelissen C, Ziemssen T. Differentiating societal costs of disability worsening in multiple sclerosis. *Journal of Neurology* 2020;**267**(4):	Exclude not an economic evaluation
Ness NH, Schriefer D, Haase R, Ettle B, Cornelissen C, Ziemssen T. Differentiating societal costs of disability worsening in multiple sclerosis. *Journal of Neurology* 2020;**267**(4):	Exclude RRMS Germany
Neuberger EE, Abbass IM, Jones E, Engmann NJ. Work Productivity Outcomes Associated with Ocrelizumab Compared with Other Disease-Modifying Therapies for Multiple Sclerosis. *Neurology & Therapy* 2021;**10**(1):	Exclude not an economic evaluation
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Citation	Reason for exclusion
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Pastor-Quiros LJ, Correa-Diaz EP. The budgetary impact of alemtuzumab in multiple sclerosis in Quito, Ecuador. Payer's perspective. *Global & Regional Health Technology Assessment* 2021;**8**	Exclude RRMS Ecuador
Perrone V, Veronesi C, Giacomini E, Citraro R, Dell'Orco S, Lena F*, et al.* The Epidemiology, Treatment Patterns and Economic Burden of Different Phenotypes of Multiple Sclerosis in Italy: Relapsing-Remitting Multiple Sclerosis and Secondary Progressive Multiple Sclerosis. *Clinical Epidemiology* 2022;**14**	Exclude not an economic evaluation
Petruzzo M, Palladino R, Nardone A, Nozzolillo A, Servillo G, Orlando V*, et al.* The impact of diagnostic criteria and treatments on the 20-year costs for treating relapsing-remitting multiple sclerosis. *Multiple Sclerosis and Related Disorders* 2020;**38**	Exclude not an economic evaluation
Pharmacoeconomic Review Report: Daclizumab (Zinbryta) [Internet]. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2017 Jul. APPENDIX 4, Reviewer Worksheets. Available from: https://www.ncbi.nlm.nih.gov/books/NBK535202/	Exclude RRMS Canada
Philbin M, Niewoehner J, Wan GJ. Clinical and Economic Evaluation of Repository Corticotropin Injection: A Narrative Literature Review of Treatment Efficacy and Healthcare Resource Utilization for Seven Key Indications. *Advances in Therapy* 2017;**34**(8):	Exclude not an economic evaluation
Piccinni C, Ronconi G, Calabria S, Dondi L, Forcesi E, Rossi E*, et al.* Healthcare resources utilisation in primary progressive multiple sclerosis. *Neurological Sciences* 2018;**39**(7):	Exclude not an economic evaluation
Piena MA, Schoeman O, Harty GT, Wong SL. Desirability and acceptability of a treatment-sequencing model in relapsing-remitting multiple sclerosis: A health technology assessment perspective. *International Journal of Technology Assessment in Health Care* 2020;**36**(2):	Exclude RRMS Netherlands
Pinheiro B, Guerreiro R, Costa J, Miguel LS. Cost-effectiveness of cladribine tablets versus fingolimod in patients with highly active relapsing multiple sclerosis in Portugal. *Journal of Medical Economics* 2020;**23**(5):	Exclude RRMS Portugal
Pinol C. [Cost-effectiveness analysis of interferon beta-1b as treatment for patients with clinically isolated syndrome suggestive of multiple sclerosis in Spain]. *Neurologia* 2016;**31**(4):	Exclude MS Spain
Pipek LZ, Mahler JV, Nascimento RFV, Apostolos-Pereira SL, Silva GD, Callegaro D. Cost, efficacy, and safety comparison between early intensive and escalating strategies for multiple sclerosis: A systematic review and meta-analysis. *Multiple Sclerosis and Related Disorders* 2023;**71**	Exclude not an economic evaluation
Pipek LZ, Mahler JV, Nascimento RFV, Becker J, Apostolos-Pereira SL, Adoni T*, et al.* The myths that drive therapeutic inertia in multiple sclerosis: a cost-effectiveness analysis of high-efficacy drugs in Brazil. *Arquivos de Neuro-Psiquiatria* 2024;**82**(1):	Exclude not an economic evaluation
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Ponzio M, Gerzeli S, Brichetto G, Bezzini D, Mancardi GL, Zaratin P*, et al.* Economic impact of multiple sclerosis in Italy: focus on rehabilitation costs. *Neurological Sciences* 2015;**36**(2):	Exclude not an economic evaluation
Poudel N, Banjara B, Kamau S, Frost N, Ngorsuraches S. Factors influencing patients' willingness-to-pay for disease-modifying therapies for multiple sclerosis. *Multiple Sclerosis and Related Disorders* 2021;**48**	Exclude not an economic evaluation
Poveda JL, Trillo JL, Rubio-Terres C, Rubio-Rodriguez D, Polanco A, Torres C. Cost-effectiveness of Cladribine Tablets and fingolimod in the treatment of relapsing multiple sclerosis with high disease activity in Spain. *Expert Review of Pharmacoeconomics & Outcomes Research* 2020;**20**(3):	Exclude MS Spain

Citation	Reason for exclusion
Prathapan V, Eipert P, Wigger N, Kipp M, Appali R, Schmitt O. Modeling and simulation for prediction of multiple sclerosis progression. *Computers in Biology & Medicine* 2024;**175**	Exclude not an economic evaluation
Purmonen T, Hakkarainen T, Tervomaa M, Ruutiainen J. Impact of multiple sclerosis phenotypes on burden of disease in Finland. *Journal of Medical Economics* 2020;**23**(2):	Exclude not an economic evaluation
Quiros LP, Ugalde R. A budget impact analysis of alemtuzumab as second-line treatment, compared with natalizumab and fingolimod, in patients previously treated with interferon beta 1b, diagnosed with active relapsing remitting multiple sclerosis, treated under the Costa Rican Social Security. [Spanish]. *Global and Regional Health Technology Assessment* 2019	Exclude RRMS Costa Rica
Rahimi F, Rasekh HR, Abbasian E, Peiravian F, Etemadifar M, Ashtari F*, et al.* Patient preferences for interferon-beta in Iran: A discrete choice experiment. *PLoS ONE* 2018;**13**	Exclude not an economic evaluation
Rahn AC, Kopke S, Kasper J, Vettorazzi E, Muhlhauser I, Heesen C. Evaluator-blinded trial evaluating nurse-led immunotherapy DEcision Coaching In persons with relapsing-remitting Multiple Sclerosis (DECIMS) and accompanying process evaluation: study protocol for a cluster randomised controlled trial. *Trials* 2015;**16**	Exclude not an economic evaluation
Ravangard R, Rezaee M, Keshavarz K, Borhanihaghighi A, Izadi S. Cost-effectiveness and cost-utility of cinnovex versus recigen in patients with relapsing-remitting multiple sclerosis in Iran. *Shiraz E Medical Journal* 2018;**19**	Exclude RRMS Iran
Reen GK, Silber E, Langdon DW. Multiple sclerosis patients' understanding and preferences for risks and benefits of disease-modifying drugs: A systematic review. *Journal of the Neurological Sciences* 2017;**375**	Exclude not an economic evaluation
Rezaee M, Izadi S, Keshavarz K, Borhanihaghighi A, Ravangard R. Fingolimod versus natalizumab in patients with relapsing remitting multiple sclerosis: a cost-effectiveness and cost-utility study in Iran. *Journal of Medical Economics* 2019;**22**(4):	Exclude RRMS Iran
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Rodriguez-Regal A, Ramos-Rua L, Anibarro-Garcia L, Lopez Real AM, Amigo-Jorrin MDC. Effectiveness of Dimethyl Fumarate in Real-World Clinical Practice and Strategy to Minimize Adverse Effects and Use of Healthcare Resources. *Patient preference & adherence* 2021;**15**	Exclude not an economic evaluation
Rojas JI, Carnero Contentti E, Alonso R, Tavolini D, Burgos M, Federico B*, et al.* Burden of treatment and quality of life in relapsing remitting multiple sclerosis patients under early high efficacy therapy in Argentina: Data from the Argentinean registry. *Multiple Sclerosis and Related Disorders* 2024;**85**	Exclude RRMS Argentina
Romero-Pinel L, Bau L, Matas E, Leon I, Juvany R, Jodar R*, et al.* Cost associated with a relapse-free patient in multiple sclerosis: A real-world health indicator. *PLoS ONE [Electronic Resource]* 2022;**17**(4):	Exclude RRMS Spain
Rot U, Horvat-Ledinek A, Sega-Jazbec S. The economic burden of multiple sclerosis. [Slovene]. *Zdravniski Vestnik* 2014;**83**	Exclude MS Slovenia
Ruggeri M, D'Ausilio A, Lo Muto R, Cottone S, Ghezzi A, Mecozzi A*, et al.* Budget Impact Analysis of Fingolimod in Relapsing Remitting Multiple Sclerosis. *Value in Health* 2014;**17**(7):	Exclude not an economic evaluation
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Citation	Reason for exclusion
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Sanchez de la Rosa R, Garcia BL, Meca Lallana J. Cost Analysis of the Use of Glatiramer Acetate Compared to Interferon-A in Patients with Relapsing-Remitting Multiple Sclerosis and Spasticity in Spain. *Value in Health* 2014;**17**(7):	Exclude RRMS Spain
Sanchez-de la Rosa R, Garcia-Bujalance L, Meca-Lallana J. Cost analysis of glatiramer acetate versus interferon-beta for relapsing-remitting multiple sclerosis in patients with spasticity: the Escala study. *Health Economics Review* 2015;**5**(1):	Exclude RRMS Spain
Sanchirico M, Caldwell-Tarr A, Mudumby P, Hashemi L, Dufour R. Treatment Patterns, Healthcare Resource Utilization, and Costs Among Medicare Patients with Multiple Sclerosis in Relation to Disease-Modifying Therapy and Corticosteroid Treatment. *Neurology & Therapy* 2019;**8**(1):	Exclude not an economic evaluation
Sandroff BM, Benedict RH, Motl RW. Nonsignificant associations between measures of inhibitory control and walking while thinking in persons with multiple sclerosis. *Archives of Physical Medicine & Rehabilitation* 2015;**96**(8):	Exclude not an economic evaluation
Sanghera S, Coast J. Measuring Quality-Adjusted Life-Years When Health Fluctuates. *Value in Health* 2020;**23**(3):	Exclude not an economic evaluation
Sawad AB, Seoane-Vazquez E, Rodriguez-Monguio R, Turkistani F. Cost-effectiveness of different strategies for treatment relapsing-remitting multiple sclerosis. *Journal of Comparative Effectiveness Research* 2017;**6**(2):	Exclude RRMS US
Schauf M, Chinthapatla H, Dimri S, Li E, Hartung DM. Economic burden of multiple sclerosis in the United States: A systematic literature review. *Journal of Managed Care & Specialty Pharmacy* 2023;**29**(12):	Exclude not an economic evaluation
Schultz TJ, Thomas A, Georgiou P, Juaton MS, Cusack L, Simon L*, et al.* Home infusions of natalizumab for people with multiple sclerosis: a pilot randomised crossover trial. *Annals of Clinical & Translational Neurology* 2021;**8**(8):	Exclude not an economic evaluation
Sicras-Mainar A, Ruiz-Beato E, Navarro-Artieda R, Maurino J. Impact on healthcare resource utilization of multiple sclerosis in Spain. *BMC Health Services Research* 2017;**17**(1):	Exclude RRMS Spain
Silverio N, Sequeira L, Meletiche D. Cost-Effectiveness of Subcutaneous Verse Intramuscular Interferon Beta-1A In Portugal Based on the Findings of Cochrane Collaboration Review of First-Line Treatments for Relapsing-Remitting Multiple Sclerosis. *Value in Health* 2014;**17**(7):	Exclude RRMS Portugal
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Simoens S. Societal economic burden of multiple sclerosis and cost-effectiveness of disease-modifying therapies. *Frontiers in neurology* 2022;**13**	Exclude not an economic evaluation
Smets I, Versteegh M, Huygens S, Corsten C, Wokke B, Smolders J. Health-economic benefits of anti-CD20 treatments in relapsing multiple sclerosis estimated using a treatment-sequence model. *Multiple Sclerosis Journal Experimental Translational & Clinical* 2023;**9**(3):	Exclude RRMS Netherlands
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Soini E, Joutseno J, Sumelahti ML. Cost-utility of First-line Disease-modifying Treatments for Relapsing-Remitting Multiple Sclerosis. *Clinical Therapeutics* 2017;**39**(3):	Exclude RRMS Finland
Stanisic S, Bertolotto A, Berto P, Di Procolo P, Morawski J. The cost-effectiveness of alemtuzumab in the management of relapse-remitting multiple sclerosis in Italy. *Global and Regional Health Technology Assessment* 2019	Exclude RRMS Italy

Citation	Reason for exclusion
Su W, Kansal A, Vicente C, Deniz B, Sarda S. The cost-effectiveness of delayed-release dimethyl fumarate for the treatment of relapsing-remitting multiple sclerosis in Canada. *Journal of Medical Economics* 2016;**19**(7):	Exclude RRMS Canada
Svensson M, Fajutrao L. Costs of formal and informal home care and quality of life for patients with multiple sclerosis in sweden. *Multiple Sclerosis International* 2014;**2014**	Exclude MS Sweden
Taheri S, Sahraian MA, Yousefi N. Cost-effectiveness of alemtuzumab and natalizumab for relapsing-remitting multiple sclerosis treatment in Iran: decision analysis based on an indirect comparison. *Journal of Medical Economics* 2019;**22**(1):	Exclude RRMS Iran
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Torabipour A, Asl ZA, Majdinasab N, Ghasemzadeh R, Tabesh H, Arab M. A study on the direct and indirect costs of multiple sclerosis based on expanded disability status scale score in khuzestan, iran. *International Journal of Preventive Medicine* 2014;**5**(9):	Exclude MS Iran
Tosh J, Dixon S, Carter A, Daley A, Petty J, Roalfe A*, et al.* Cost effectiveness of a pragmatic exercise intervention (EXIMS) for people with multiple sclerosis: economic evaluation of a randomised controlled trial. *Multiple Sclerosis* 2014;**20**(8):	Exclude intervention
Touchette DR, Durgin TL, Wanke LA, Goodkin DE. A cost-utility analysis of mitoxantrone hydrochloride and interferon beta-1b in the treatment of patients with secondary progressive or progressive relapsing multiple sclerosis. *Clinical Therapeutics* 2003;**25**(2): 611-634	Exclude SPMS US
van Eijndhoven E, Brauer M, Kee R, MacEwan J, Mucha L, Wong SL*, et al.* Modeling the impact of patient treatment preference on health outcomes in relapsing-remitting multiple sclerosis. *Journal of medical economics* 2020;**23**(5): 474-483	Exclude Intervention
van Mastrigt GA, Evers SM, Heerings M, Visser LH, Ruimschotel RP, Hussaarts A*, et al.* An economic evaluation attached to a single-centre, parallel group, unmasked, randomized controlled trial of a 3-day intensive social cognitive treatment (can do treatment) in patients with relapsing remitting multiple sclerosis and low disability. *Journal of Medical Economics* 2019;**22**(10):	Exclude RRMS Netherlands
Vandhuick O, Payet M, Preaud E, Lortet-Tieulent J, Raguideau F, Chevreuil O*, et al.* Economic burden of highly active relapsing-remitting multiple sclerosis patients in the French national health insurance database. *Expert Review of Pharmacoeconomics & Outcomes Research* 2021;**21**(5):	Exclude RRMS France
Veauthier C, Hasselmann H, Gold SM, Paul F. The Berlin Treatment Algorithm: recommendations for tailored innovative therapeutic strategies for multiple sclerosis-related fatigue. *The EPMA Journal* 2016;**7**	Exclude not an economic evaluation
Versteegh MM, Huygens SA, Wokke BWH, Smolders J. Effectiveness and Cost-Effectiveness of 360 Disease-Modifying Treatment Escalation Sequences in Multiple Sclerosis. *Value in Health* 2022;**25**(6): 984-991	Exclude RRMS Netherlands
Viktor Chirikov, Ingrid Ma, Namita Joshi, Dipen Patel, Alden Smith, Cindy Giambrone, et al. Cost-Effectiveness of Alemtuzumab in the Treatment of Relapsing Forms of Multiple Sclerosis in the United States. Value in Health 2019;22(6):	Exclude RRMS US
Visser LA, Folcher M, Delgado Simao C, Gutierrez Arechederra B, Escudero E, Uyl-de Groot CA*, et al.* The Potential Cost-Effectiveness of a Cell-Based Bioelectronic Implantable Device Delivering Interferon-beta1a Therapy Versus Injectable Interferon-beta1a Treatment in Relapsing-Remitting Multiple Sclerosis. *PharmacoEconomics* 2022;**40**(1):	Exclude RRMS Netherlands
Walker A, Watson C, Alexopoulos ST, Deniz B, Arnold R, Bates D. A benefit-risk analysis of natalizumab in the treatment of patients with multiple sclerosis when considering the risk of progressive multifocal leukoencephalopathy. *Current Medical Research & Opinion* 2014;**30**(4):	Exclude RRMS Austria
Walter E, Berger T, Bajer-Kornek B, Deisenhammer F. Cost-utility analysis of alemtuzumab in comparison with interferon beta, fingolimod, and natalizumab treatment for relapsing-remitting multiple sclerosis in Austria. *Journal of Medical Economics* 2019;**22**(3):	Exclude RRMS Austria

Citation	Reason for exclusion
Walter E, Deisenhammer F. Socio-economic aspects of the testing for antibodies in MS-patients under interferon therapy in Austria: a cost of illness study. *Multiple Sclerosis and Related Disorders* 2014;**3**(6):	Exclude MS Austria
Wan GJ, Chopra I, Niewoehner J, Hunter SF. Cost per response analysis of repository corticotropin injection versus other alternative treatments for acute exacerbations of multiple sclerosis. *Drugs in Context* 2020;**9**	Exclude MS US
Watson C, Prosser C, Braun S, Landsman-Blumberg PB, Gleissner E, Naoshy S. Health care resource utilization before and after natalizumab initiation among patients with multiple sclerosis in Germany. *Clinicoeconomics & Outcomes Research* 2017;**9**	Exclude RRMS Germany
Watson C, Prosser C, Braun S, Landsman-Blumberg PB, Gleissner E, Naoshy S. Health care resource utilization before and after natalizumab initiation among patients with multiple sclerosis in Germany. *Clinicoeconomics & Outcomes Research* 2017;**9**	Exclude not an economic evaluation
Wilkinson SN, Dougall C, Kinsey-Henderson AE, Searle RD, Ellis RJ, Bartley R. Development of a time-stepping sediment budget model for assessing land use impacts in large river basins. *Science of the Total Environment* 2014;**468**	Exclude not an economic evaluation
Wilson S, Calocer F, Rollot F, Fauvernier M, Remontet L, Tron L*, et al.* Effects of socioeconomic status on excess mortality in patients with multiple sclerosis in France: A retrospective observational cohort study. *The Lancet Regional Health Europe* 2023;**24**	Exclude RRMS France
Wiyani A, Badgujar L, Khurana V, Adlard N. How have Economic Evaluations in Relapsing Multiple Sclerosis Evolved Over Time? A Systematic Literature Review. *Neurology and Therapy* 2021;**10**(2): 557-583	Exclude not an economic evaluation
Wiyani A, Badgujar L, Khurana V, Adlard N. How have Economic Evaluations in Relapsing Multiple Sclerosis Evolved Over Time? A Systematic Literature Review. *Neurology & Therapy* 2021;**10**(2):	Exclude not an economic evaluation
Xu Y, Mao N, Chirikov V, Du F, Yeh YC, Liu L*, et al.* Cost-effectiveness of Teriflunomide Compared to Interferon Beta-1b for Relapsing Multiple Sclerosis Patients in China. *Clinical Drug Investigation* 2019;**39**(3):	Exclude RRMS China
Yadlowsky S, Pellegrini F, Lionetto F, Braune S, Tian L. Estimation and Validation of Ratio-Based Conditional Average Treatment Effects Using Observational Data. *Journal of the American Statistical Association* 2021;**116**(533):	Exclude not an economic evaluation
Yang H, Duchesneau E, Foster R, Guerin A, Ma E, Thomas NP. Cost-effectiveness analysis of ocrelizumab versus subcutaneous interferon beta-1a for the treatment of relapsing multiple sclerosis. *Journal of Medical Economics* 2017;**20**(10):	Exclude RMS US
Zarco LA, Millan SP, Londono D, Parada L, Taborda A, Borda MG. [The cost-effectiveness of interferon beta treatment in patients with a clinically isolated syndrome in Colombia]. *Biomedica* 2014;**34**(1):	Exclude MS Colombia
Zarghami A, Fuh-Ngwa V, Claflin SB, Simpson-Yap S, Lucas R, Dear K*, et al.* Changes in employment status over time in multiple sclerosis following a first episode of central nervous system demyelination, a Markov multistate model study. *European Journal of Neurology* 2024;**31**	Exclude wrong population
Zhang X, Hay JW, Niu X. Cost effectiveness of fingolimod, teriflunomide, dimethyl fumarate and intramuscular interferon-beta1a in relapsing-remitting multiple sclerosis. *CNS Drugs* 2015;**29**(1):	Exclude RRMS China
Ziemssen T, Kurzeja A, Muresan B, Haas JS, Alexander J, Driessen MT. Real-world patient characteristics, treatment patterns and costs in relapsing multiple sclerosis patients treated with glatiramer acetate, dimethyl fumarate or teriflunomide in Germany. *Neurodegenerative Disease Management* 2022;**12**(2):	Exclude RRMS Germany
Zimmermann M, Brouwer E, Tice JA, Seidner M, Loos AM, Liu S*, et al.* Disease-Modifying Therapies for Relapsing-Remitting and Primary Progressive Multiple Sclerosis: A Cost-Utility Analysis. *CNS Drugs* 2018;**32**(12):	Exclude RRMS Germany

Appendix 3
Included study details

Study characteristics

Table 46 Overview of studies included in the review

Study Name	Population	Number enrolled	Duration (median follow-up)	Study Phase	Funding Sources	Study Location	MS Criteria	Previous treatment	Interventions evaluated
ADVANCE[80]	RRMS	1512	48 weeks (NR)	Phase III	Industry	183 sites in 26 countries	McDonald	Yes	Peginterferon beta 1a SC125
									Placebo
AFFIRM[77]	RRMS	943	2 years (NR)	Phase III	Industry	99 sites in Europe, North America, and New Zealand	McDonald	Yes	Natalizumab IV300
									Placebo
ANTELOPE[76]	RRMS	265	48 weeks (NR)	Phase III	Industry	48 sites in 7 countries	McDonald	Yes	Natalizumab IV300
									Natalizumab biosimilar
APOLITOS[69]	RRMS	64	24 weeks (NR)	Phase II	Industry	Japan and Russia	McDonald	Yes	Ofatumumab SC20
									Placebo
ASCLEPIOS I[68]	RRMS (94%)	927	30 months (1.5 years)	Phase III	Industry	385 sites in 37 countries	McDonald	Yes	Ofatumumab SC20
									Teriflunomide O14
ASCLEPIOS II[68]	RRMS (94%)	955	30 months (1.6 years)	Phase III	Industry		McDonald	Yes	Ofatumumab SC20
									Teriflunomide O14
ASSESS[81]	RRMS	1064	12 months (NR)	Phase III	Industry	127 sites in 6 countries	McDonald	Yes	Fingolimod O0.5
									Glatiramer acetate SC20
BEYOND[82]	RRMS	1345	2 years (NR)	Phase III	Industry	98 centres in 26 countries worldwide	McDonald	No	Interferon beta 1b SC250
									Glatiramer acetate SC20
Calabrese 2012[83]	RRMS	165	2 years (NR)	Phase IV	Industry	Italy	McDonald	No	Interferon beta 1a SC44
									Interferon beta 1a IM30
									Glatiramer acetate SC20
CAMMS223[84]	RRMS	334	36 months (NR)	Phase II	Industry	49 sites in Europe and the United States.	McDonald	No	Interferon beta 1a SC44
									Alemtuzumab IV12

Study Name	Population	Number enrolled	Duration (median follow-up)	Study Phase	Funding Sources	Study Location	MS Criteria	Previous treatment	Interventions evaluated
CARE-MS I[85]	RRMS	581	2 years (NR)	Phase III	Industry	101 sites in 16 countries	McDonald	No	Alemtuzumab IV12
									Interferon beta 1a SC44
CARE-MS II[71]	HARRMS	840	2 years (NR)	Phase III	Industry	194 sites in 23 countries	McDonald	Yes	Interferon beta 1a SC44
									Alemtuzumab IV12
CLARITY[86]	RRMS + HARRMS	1326	96 weeks (NR)	Phase III	Industry	155 sites in 32 countries	McDonald	Yes	Cladribine O3.5
									Placebo
CombiRx[87]	RRMS	1008	36 months (NR)	Phase III	Mixed	68 sites in USA and Canada	Poser or McDonald	Yes	Glatiramer acetate SC20
									Interferon beta 1a IM30
CONFIDENCE[88]	RRMS	861	6 months (NR)	Phase IV	Industry	14 countries	McDonald	Yes	Glatiramer acetate SC40
									Glatiramer acetate SC20
CONFIRM[89]	RRMS + HARRMS	1430	2 years (NR)	Phase III	Industry	200 sites in 28 countries	McDonald	Yes	Glatiramer acetate SC20
									Placebo
Copolymer 1 Multiple Sclerosis Study Group[90]	RRMS	251	2 years (NR)	Phase III	Mixed	USA	Poser	No	Glatiramer acetate SC20
									Placebo
Etemedifar 2006[91]	RRMS	90	2 years (NR)	NR	Not reported	Iran	Poser	No	Interferon beta 1b SC250
									Interferon beta 1a IM30
									Interferon beta 1a SC44
European/Canadian glatiramer acetate study group[92]	RRMS	239	9 months (NR)	NR	Industry	29 sites in 6 European countries and Canada	Poser	No	Glatiramer acetate SC20
									Placebo
EVIDENCE[93]	RRMS	677	48 weeks (NR)	NR	Industry	56 sites (15 in Europe, 5 in Canada, and 36in the United States)	Poser	No	Interferon beta 1a SC44
									Interferon beta 1a IM30
FREEDOMS[74]	RRMS + HARRMS	1272	2 years (NR)	Phase III	Industry	138 sites in 22 countries.	McDonald	Yes	Fingolimod O0.5
									Placebo
FREEDOMS II[73]		1083		Phase III	Industry		McDonald	Yes	Fingolimod O0.5

Study Name	Population	Number enrolled	Duration (median follow-up)	Study Phase	Funding Sources	Study Location	MS Criteria	Previous treatment	Interventions evaluated
	RRMS + HARRMS		24 months (NR)			117 sites in eight countries			Placebo
GALA[94]	RRMS	1404	1 year (NR)	Phase III	Industry	142 sites in 17 countries	McDonald	Yes	Glatiramer acetate SC40
									Placebo
GATE[95]	RRMS	796	9 months (NR)	Phase III	Industry	18 sites in 17 countries	McDonald	Yes	Glatiramer acetate SC20
									Placebo
GOLDEN[96]	RRMS	157	18 months (NR)	NR	Industry	36 sites 28 in Italy and 8 in Germany	McDonald	Yes	Fingolimod O0.5
									Interferon beta 1b SC250
IMPROVE[98]	RRMS	180	16 weeks double-blind then 24 week rater-blind (NR)	Phase III	Industry	International	McDonald	No	Interferon beta 1a SC44
									Placebo
INCOMIN[99]	RRMS	188	2 years (NR)	NR	Non-industry	15 sites in Italy	Poser	No	Interferon beta 1a IM30
									Interferon beta 1b SC250
IFNB Multiple Sclerosis Study Group[97]	RRMS	372	Unclear (NR)	NR	Industry	United States and Canada	Poser	No	Interferon beta 1b SC250
									Placebo
Kappos 2011[100]	RRMS	220	48 weeks (NR)	Phase II	Industry	International	McDonald	Yes	Ocrelizumab IV600
									Interferon beta 1a IM30
									Placebo
MIST[72]	HARRMS	110	Enrolment between 2005-2016, with final follow-up in 2018 (2 years)	NR	Non-industry	International	McDonald	Yes	AHSCT
									iDMT
	RRMS	301		Phase III	Mixed	USA	Poser	Yes	Interferon beta 1a IM30

Study Name	Population	Number enrolled	Duration (median follow-up)	Study Phase	Funding Sources	Study Location	MS Criteria	Previous treatment	Interventions evaluated
Multiple Sclerosis Collaborative Research Group[105]			2 years (NR)						Placebo
OPERA I[67]	RRMS + HARRMS	821	96 weeks (NR)	Phase III	Industry	141 trial sites across 32 countries	McDonald	Yes	Ocrelizumab IV600
									Interferon beta 1a SC44
OPERA II[67]	RRMS + HARRMS	835	96 weeks (NR)	Phase III	Industry	166 trial sites across 24 countries	McDonald	Yes	Ocrelizumab IV600
									Interferon beta 1a SC44
OPTIMUM[70]	RRMS (97%)	1133	108 weeks (NR)	Phase III	Industry	162 sites across 28 countries	McDonald	Yes	Ponesimod O20
									Teriflunomide O14
PEGINTEGRITY[65]	RRMS	168	96 weeks (NR)	Phase III	Industry	9 sites in Iran	McDonald	No	Peginterferon beta 1a SC125
									Interferon beta 1a IM30
Ponesimod Phase II study Group[101]	RRMS	387	24 weeks (NR)	Phase II	Industry	94 sites in 23 countries	McDonald	Yes	Ponesimod O20
									Placebo
PRISMS[102]	RRMS	560	2 years (NR)	NR	Industry	22 sites in 9 countries	Poser	No	Interferon beta 1a SC22
									Interferon beta 1a SC44
									Placebo
REGARD[103]	RRMS	764	96 weeks (NR)	Phase IV	Industry	81 sites in 14 countries	McDonald	Yes	Interferon beta 1a SC44
									Glatiramer acetate SC20
REVEAL[78]	RRMS	111	52 weeks (Natalizumab 40.1 weeks; Fingolimod 36.7 weeks)	Phase IV	Industry	43 sites in nine countries.	McDonald	Yes	Natalizumab IV300
									Fingolimod O0.5
Saida 2012[104]	RRMS (98%)	171	6 months (NR)	Phase II	Industry	43 centres in Japan	McDonald	No	Fingolimod O0.5
									Placebo
Saida 2017[79]		94		Phase II	Industry	25 sites in Japan	McDonald	Yes	Natalizumab IV300

Study Name	Population	Number enrolled	Duration (median follow-up)	Study Phase	Funding Sources	Study Location	MS Criteria	Previous treatment	Interventions evaluated
	RRMS and close to HARRMS		24 weeks (NR)						Placebo
TRANSFORMS[75]	RRMS + HARRMS	1291	12 months (NR)	Phase III	Industry	172 sites in 18 countries.	McDonald	Yes	Fingolimod O0.5
									Interferon beta 1a IM30

Included studies and reports

Table 47 Studies included in the review showing primary and related reports and whether additional data were extracted from related reports

Study Name	Report	Additional Data report
ADVANCE	Primary report[80]	NA
	Related report - data extracted[204]	Quality of life data
	Related report - no relevant data[205]	no evidence of disease - NEDA data
	Related report - no relevant data[206]	Post hoc analysis of evolution of MRI lesions
	Related report - no relevant data[207]	Pharmacokinetics and pharmacodynamics data
	TA624[32]	Additional data on disease progression
AFFIRM	Primary report[77]	NA
	Related report - data extracted[208]	Reports on AFFIRM and SENTINEL EDSS
	Related report - no relevant data[209]	Visual outcomes
	Related report - no relevant data[210]	Free from disease activity
	Related report - no relevant data[211]	Data in patients who have relapsed
	Related report - no relevant data[212]	MRI outcomes
	Related report - no relevant data[213]	MRI outcomes
	Trial Registry Entry[214]	NA
AFFIRM/SENTINEL	Synthesis across related studies[215]	Visual outcomes
	Synthesis across related studies[216]	Participants of African descent
	Synthesis across related studies[217]	Subgroup analyses
	TA127[34]	Additional data on disease progression; additional potentially relevant data on disease progression redacted
AFFIRM/TIMER	Synthesis across related studies[218]	Ambulation outcomes
ANTELOPE	Primary report[76]	NA
	Trial Registry Entry[219]	NA
APOLITOS	Primary report[69]	NA
ASCLEPIOS I/II	Primary report[68]	NA
	Related report - no relevant data[220]	Sub analysis on treatment naïve patients

Study Name	Report	Additional Data report
	Trial registry[221]	NA
	TA699[41]	No additional data – data for highly active population redacted
ASSESS	Primary report[81]	NA
	Trial Registry Entry[222]	NA
BEYOND	Primary report[82]	NA
	Related report - no relevant data[223]	Additional MRI outcomes (black hole development)
Calabrese 2012	Primary report[83]	NA
CAMMS223	Primary report[84]	NA
	Related report - no relevant data[224]	Subgroup analyses, freedom from disease activity, sustained disability reduction
	Related report - no relevant data[225]	Follow-up of 6 patients with thrombocytopenia
	Related report - no relevant data[226]	Thyroid dysfunction outcome data
	Related report - no relevant data[227]	individual functional scores of EDSS outcomes
	Related report - no relevant data[228]	Visual outcomes
	Trial Registry Entry[229]	NA
	TA312[39]	No additional data; data on QoL redacted
CARE-MS I	Primary report[85]	NA
	Trial Registry Entry[230]	NA
	Trial Registry Entry[231]	NA
	TA312[39]	No additional data
CARE-MS II	Primary report[71]	NA
	Related report - no relevant data[232]	QoL Data
	Related report - no relevant data[233]	Additional EDSS data
	Trial Registry Entry[234]	NA
	Trial Registry Entry[235]	NA
	Trial Registry Entry[236]	NA
	TA312[39]	No additional data
CARE-MS I/II	Synthesis across related studies[237]	Additional MRI outcomes
	Synthesis across related studies[238]	QoL data
	Synthesis across related studies[239]	Neutropenia

Study Name	Report	Additional Data report
	Synthesis across related studies[240]	Post-hoc analysis looking at age
	Synthesis across related studies[241]	QoL - FAMS only
	Synthesis across related studies[242]	Safety data in Russian patients
CLARITY	Primary report[86]	NA
	Related report - data extracted[243]	QoL data
	Related report - data extracted[244]	Additional data on freedom from disease activity
	Related report - highly active population[245]	Data extracted for this population
	Related report - no relevant data[246]	Additional MRI outcomes
	Related report - no relevant data[247]	Additional safety data
	Related report - no relevant data[248]	Additional MRI outcomes
	Related report - no relevant data[249]	Brain volume changes
	Related report - no relevant data[250]	Relapses in main and extension trial
	Related report - no relevant data[251]	Additional data on highly active subgroup
	Related report - no relevant data[252]	Cardiac outcomes
	Related report - no relevant data[253]	Subgroup data including rapidly evolving severe MS
	Trial Registry Entry[254]	NA
	Trial Registry Entry[255]	NA
	TA616[38]	No additional data
CLARITY/CARE-MS-I	Synthesis across related studies[256]	lymphocyte data
CombiRx	Primary report[87]	NA
	Related report - no relevant data[257]	Risk factors for early treatment failure
	Related report - no relevant data[258]	Designs and baseline characteristics
	Related report - no relevant data[259]	Imaging biomarker data
CONFIDENCE	Primary report[88]	NA
CONFIRM	Primary report[89]	NA
	Related report - data extracted[260]	quality of life data
	Related report - highly active population[261]	subgroup analyses

Study Name	Report	Additional Data report
	Related report - no relevant data[262]	Effect of DF on MRI measures
	Synthesis across related studies[263]	Effect of DF on prior interferon users
	Synthesis across related studies[264]	Effect of DF on no evidence of disease
	Trial Registry Entry[265]	NA
Copolymer 1 Multiple Sclerosis Study Group	Primary report[90]	NA
	Related report - no relevant data[266]	Area under disability time curves
	Related report - no relevant data[267]	Neuropsychological outcomes
	Trial Registry Entry[268]	NA
Etemedifar 2006	Primary report[91]	NA
European/Canadian glatiramer acetate study group	Primary report[92]	NA
	Related report - no relevant data[269]	Additional MRI Outcomes
EVIDENCE	Primary report[93]	
	Related report - data extracted[270]	outcomes at 16 months
	Related report - data extracted[271]	Data for comparative phase and crossover phase
	Related report - no relevant data[272]	data on NEDA
	Related report - no relevant data[273]	specific safety and tolerability data
	Related report - no relevant data[274]	data after crossover
	Related report - no relevant data[275]	MRI T2 burden of disease data
FREEDOMS	Primary report[74]	NA
	Related report - data extracted[276]	Highly active subgroup data
	Related report - no relevant data[277]	Post hoc analysis of subgroups based on previous treatments
	Related report - no relevant data[278]	Additional MRI data
	Trial Registry Entry[279]	NA
	Trial Registry Entry[280]	NA
	TA254[40]	Baseline data for HA population; redacted data on: baseline relapse rate, HR for disability progression in highly active population and EQ-5D data
FREEDOMS II	Primary report[73]	NA
	Related report - no relevant data[281]	Corrections to paper
	Trial Registry Entry[282]	NA

Study Name	Report	Additional Data report
	Trial Registry Entry[283]	NA
FREEDOMS/ FREEDOMS II	Synthesis across related studies[284]	MRI brain volume
	Synthesis across related studies[110]	Highly active subgroup
	Synthesis across related studies[285]	MRI outcomes
	Synthesis across related studies[286]	Early (3 and 6 months) outcomes
FREEDOMS/ FREEDOMS II/ TRANSFORMS	Synthesis across related studies[287]	Hispanic patients
	Synthesis across related studies[288]	Relapse rates in different patient subgroups
FREEDOMS/ TRANSFORMS	Synthesis across related studies[289]	Hungarian poster with clinical and MRI outcomes
GALA	Primary report[94]	NA
	Related report - data extracted[290]	post-hoc analysis of the study but think it is just focusing on a russian patient subset?
	Related report - no relevant data[291]	Timing of efficacy onset
	Related report - no relevant data[292]	looks at total t1 lesions vs t1 non enhanced lesions
	Trial Registry Entry[293]	NA
GATE	Primary report[95]	NA
	Trial Registry Entry[294]	NA
GOLDEN	Primary report[96]	NA
	Trial Registry Entry[295]	NA
	Trial Registry Entry[296]	NA
IFNB Multiple Sclerosis Study Group	Primary report[97]	NA
	Related report - data extracted[297]	Additional MRI data
	Related report - data extracted[298]	Additional MRI data
	Related report - no relevant data[299]	Additional MRI data
	Related report - no relevant data[300]	Additional MRI data
IMPROVE	Primary report[98]	NA
	Related report - data extracted[301]	baseline data
	Related report - no relevant data[302]	Other MRI outcomes
	Trial Registry Entry[303]	NA
	Trial Registry Entry[304]	NA

Study Name	Report	Additional Data report
INCOMIN	Primary report[99]	NA
	Related report - no relevant data[305]	Additional MRI outcomes
Kappos2011	Primary report[100]	NA
	Trial Registry Entry[306]	NA
	Trial Registry Entry[307]	NA
MIST	Primary report[72]	NA
	Trial Registry Entry[308]	NA
Multiple Sclerosis Collaborative Research Group	Primary report[105]	NA
	Related report - no relevant data[309]	Baseline details
	Related report - no relevant data[310]	Additional data on disability
OPERA I/II	Primary report[67]	NA
	Synthesis across related studies[311]	Brain volume
	Synthesis across related studies[312]	MRI outcomes
	Synthesis across related studies[313]	Data for participants of African descent
	Synthesis across related studies[314]	Risk of requiring walking aid after 6.5 years - open label extension
	Synthesis across related studies[315]	Infusion related reactions
	Synthesis across related studies[316]	Data for highly active disease
	Synthesis across related studies[317]	Subgroup of patients with increased disability at baseline
	NICE TA533[33]	Additional data on highly active disease (combined across both trials); redacted data on EQ-5D
OPTIMUM	Primary report[70]	NA
	Related report - no relevant data [318]	Subgroup analysis in women
	Trial registry entry[319]	NA
	TA767[42]	No additional data – data for highly active population redacted
PEGINTEGRITY	Primary report[65]	NA
	Trial Registry Entry[320]	NA
Ponesimod Phase II study Group	Primary report[101]	NA
	Related report - no relevant data[321]	Erratum relating to Figure
	Synthesis across related studies[322]	Core and extension studies
	Trial Registry Entry[323]	NA

Study Name	Report	Additional Data report
PRISMS	Primary report[102]	NA
	Related report - data extracted[324]	MRI outcomes
	Related report - data extracted[325]	NEDA data
	Related report - no relevant data[326]	Erratum relating to author COI
	Related report - no relevant data[327]	Additional EDSS outcomes
	Related report - no relevant data[328]	Additional EDSS outcomes
	Related report - no relevant data[329]	Depression outcomes
PRISMS/SPECTRIMS	Synthesis across related studies[330]	Posthoc analysis of combined data
	Synthesis across related studies[331]	MRI outcomes
REGARD	Primary report[103]	NA
	Trial Registry Entry[332]	NA
REVEAL	Primary report[78]	NA
	Trial Registry Entry[333]	NA
	Trial Registry Entry[334]	NA
Saida 2012	Primary report[104]	NA
Saida 2017	Primary report[79]	NA
	Trial Registry Entry[335]	NA
	Related report - no relevant data[336]	subanalysis of patients who achieved no evidence of disease
TRANSFORMS	Primary report[75]	NA
	Related report - no relevant data[337]	MRI brain volume outcomes
	Related report - no relevant data[338]	Highly active and other subgroup data but not in format for inclusion
	Related report - no relevant data[339]	subgroup analysis
	Trial Registry Entry[340]	NA
	Trial Registry Entry[341]	NA

Baseline characteristics

Table 48 Baseline participant details (RRMS population)

Study Name	Treatment arm	N	Age (sd)	% Female	Years from diagnosis (SD)	EDSS (SD)	% White	% Black	% Asian	% Other	Annual Relapse rate (SD)	% treated	Previous treatments
ADVANCE[80]	Placebo	500	36.3 (9.7)	72	3.5(4.6)	2.4 (1.2)	82	0.6	11	6	1.6(0.7)	7	DMT
	Peginterferon beta 1a SC125	512	36.9 (9.8)	71	4(5.1)	2.5 (1.3)	81	0.58	12	7	1.6(0.7)	8	
AFFIRM[77]	Natalizumab IV300	627	35.6 (8.5)	72	NR(NR)	2.3 (1.2)	96	NR	NR	4	1.5(0.9)	9	interferon beta-1a interferon beta-1b or glatiramer acetate
	Placebo	315	36.7 (7.8)	67	NR(NR)	2.3 (1.2)	94	NR	NR	6	1.5(0.8)	8	
ANTELOPE[76]	Natalizumab biosimilar	131	36.8 (9.1)	64.1	5.3(4.7)	3.4 (1.1)	100	0	0	0	1.4(0.7)	NR	NR
	Natalizumab IV300	133	36.6 (9.7)	58.6	5.3(4.8)	3.2 (1.2)	100	0	0	0	1.4(0.6)	NR	
APOLITOS[69]	Ofatumumab SC20	43	35 (9.5)	83.7	5.1(6.3)	2.2 (1)	51.2	NR	48.8	NR	1.6(0.9)	67	interferon beta; glatiramer; dimethyl fumarate; fingolimod; natalizumab; other DMTS
	Placebo	21	35.5 (8.9)	90.5	6(6.4)	2.2 (1.3)	47.6	NR	52.4	NR	1.2(0.7)	71	
ASCLEPIOS I[68]	Ofatumumab SC20	465	38.9 (8.8)	68	5.8 (6.1)	3.0 (1.4)	88	3	3	5	1.2(0.6)	59	interferon beta, glatiramer acetate, dimethyl fumarate,
	Teriflunomide O14	462	37.8 (9.0)	69	5.6 (6.2)	3.0 (1.4)	89	4	4	3	1.3(0.7)	61	
ASCLEPIOS II[68]	Ofatumumab SC20	481	38.0 (9.3)	66	5.6 (6.4)	2.9 (1.3)	87	3	4	4	1.3(0.7)	60	

Study Name	Treatment arm	N	Age (sd)	% Female	Years from diagnosis (SD)	EDSS (SD)	% White	% Black	% Asian	% Other	Annual Relapse rate (SD)	% treated	Previous treatments
	Teriflunomide O14	474	38.2 (9.5)	67	5.5 (6.0)	2.9 (1.4)	88	4	4	3	1.3(0.7)	62	natalizumab, B-cell therapy, lanquinimod, other DMT
ASSESS[81]	Fingolimod O0.5	352	40.3 (11.1)	75	4.3(5.9)	2.7 (1.5)	76.1	9.7	0	11.9	1.4(0.8)	52	NR
	Glatiramer acetate SC20	342	39.6 (10.8)	73.7	4.7(6.2)	2.7 (1.4)	71.1	12	0	14.3	1.4(0.8)	55	
BEYOND[82]	Interferon beta 1b SC250	897	35.8 (IQR 28-43)	70	5.3(NR)	2.4 (IQR 1.5-3.0)	93	NR	NR	NR	1.6(NR)	0	None
	Glatiramer acetate SC20	448	35.2 (IQR 27-43)	68	5.1(NR)	2.3 (IQR 1.5-3.1)	91	NR	NR	NR	1.6(NR)	0	
Calabrese 2012[83]	Interferon beta 1a SC44	46	35.9 (9.1)	69.5	5.7(4.9)	1.9 (1)	NR	NR	NR	NR	1.2(0.6)	NR	NR
	Interferon beta 1a IM30	47	34.8 (9.6)	68	5.3(5.1)	1.9 (0.8)	NR	NR	NR	NR	1.2(0.7)	NR	
	Glatiramer acetate SC20	48	38.9 (10.2)	72.9	5.5(6.1)	2.1 (1.1)	NR	NR	NR	NR	1.3(0.7)	NR	
CAMMS223[84]	Interferon beta 1a SC44	111	32.8 (8.8)	64	NR(NR)	1.9 (0.8)	90.1	NR	NR	NR	NR	0	None
	Alemtuzumab IV12	112	31.9 (8.0)	64.3	NR(NR)	1.9 (0.7)	91.1	NR	NR	NR	NR	0	
CARE-MS I[85]	Interferon beta 1a SC44	187	33.2 (8.5)	65	2(1.3)	2 (0.8)	96	NR	NR	NR	1.8(0.8)	0	None
	Alemtuzumab IV12	376	33 (8.0)	65	2.1(1.4)	2 (0.8)	94	NR	NR	NR	1.8(0.8)	0	
CLARITY[86]	Placebo	437	38.7 (9.9)	65.9	8.9(7.4)	2.9 (1.3)	98.2	0.2	NR	1.6	NR	33	interferon beta 1a, interferon beta 1b, glatiramer acetate
	Cladribine O3.5	433	37.9 (10.3)	68.8	7.9(7.2)	2.8 (1.2)	98.2	0.5	NR	1.4	NR	32	

Study Name	Treatment arm	N	Age (sd)	% Female	Years from diagnosis (SD)	EDSS (SD)	% White	% Black	% Asian	% Other	Annual Relapse rate (SD)	% treated	Previous treatments
CombiRx[87]	Glatiramer acetate SC20	259	39 (9.5)	71.4	1(2.9)	1.9 (1.2)	90.3	NR	NR	NR	1.6(0.7)	NR	NR
	Interferon beta 1a IM30	250	37.6 (10.2)	69.2	1.4(4)	2 (1.2)	84.8	NR	NR	NR	1.7(0.9)	NR	
CONFIDENCE[88]	Glatiramer acetate SC40	431	41 (11.2)	66.8	5.7(6.5)	2.2 (1.3)	83.3			16.7	0.8(0.9)	60	Any DMT
	Glatiramer acetate SC20	430	40.1 (10.7)	71.4	5.6(6.3)	2.1 (1.3)	84.4			15.6	0.7(0.7)	59	
CONFIRM[89]	Placebo	363	36.9 (9.2)	69	4.8(5)	2.6 (1.2)	84	2	8	6	1.4(0.8)	31	interferon beta 1a, interferon beta 1b, glatiramer, natalizumab
	Glatiramer acetate SC20	350	36.7 (9.1)	71	4.4(4.7)	2.6 (1.2)	83	3	7	7	1.4(0.6)	29	
Copolymer 1 Multiple Sclerosis Study Group[90]	Glatiramer acetate SC20	125	34.6 (6)	70.4	7.3(4.9)	2.8 (1.2)	94.4	NR	NR	5.6	1.5(0.7)	NR	NR
	Placebo	126	34.3 (6.5)	76.2	6.6(5.1)	2.4 (1.3)	93.6	NR	NR	6.3	1.5(0.6)	NR	
Etemedifar 2006[91]	Interferon beta 1b SC250	30	NR (NR)	30.9	3.7(2.3)	NR (NR)	NR	NR	NR	NR	2.2(0.7)	NR	NR
	Interferon beta 1a IM30	30	NR (NR)	35.3	2.9(2.3)	NR (NR)	NR	NR	NR	NR	2.0(0.8)	NR	
	Interferon beta 1a SC44	30	NR (NR)	33.8	3.0(2.2)	NR (NR)	NR	NR	NR	NR	2.4(1.0)	NR	
European/ Canadian glatiramer acetate study group[92]	Glatiramer acetate SC20	119	34.1 (7.4)	NR	7.9(5.5)	2.3 (1.1)	NR	NR	NR	NR	1.4(0.9)	NR	NR
	Placebo	120	34 (7.5)	NR	8.3(5.5)	2.4 (1.2)	NR	NR	NR	NR	1.2(0.7)	NR	
EVIDENCE[93]	Interferon beta 1a SC44	339	38.3 (NR)	74.9	4.0(6.5)	2.0 (2.3)	92.3	NR	NR	NR	2.0(2.6)	0	None

Study Name	Treatment arm	N	Age (sd)	% Female	Years from diagnosis (SD)	EDSS (SD)	% White	% Black	% Asian	% Other	Annual Relapse rate (SD)	% treated	Previous treatments
	Interferon beta 1a IM30	338	37.4 (NR)	74.6	4.1(6.7)	2.0 (2.3)	89.6	NR	NR	NR	2.0(2.6)	0	
FREEDOMS[74]	Fingolimod O0.5	425	36.6 (8.8)	69.6	8.0(6.6)	2.3 (1.3)	NR	NR	NR	NR	1.5(0.8)	43	Interferon beta 1a, interferon beta 1b, glatiramer acetate,
	Placebo	418	37.2 (8.6)	71.3	8.1(6.4)	2.5 (1.3)	NR	NR	NR	NR	1.4(0.7)	40	
FREEDOMS II[73]	Fingolimod O0.5	358	40.6 (8.4)	77	10.4(8.0)	2.4 (1.3)	NR	NR	NR	NR	1.4(0.9)	74	Interferon beta 1a, interferon beta 1b, glatiramer acetate, natalizumab
	Placebo	355	40.1 (8.4)	81	10.6(7.9)	2.4 (1.3)	NR	NR	NR	NR	1.5(0.9)	73	
GALA[94]	Glatiramer acetate SC40	943	37.4 (9.4)	68	NR	2.8 (1.2)	97.1	1.3	0.2	1.4	1.3(0.6)	14	Prior DMT treatment
	Placebo	461	38.1 (9.2)	67.9	NR(NR)	2.7 (1.2)	98.7	0.7	0	0.6	1.3(0.6)	14	
GATE[95]	Glatiramer acetate SC20	357	33.8 (9)	66.7	6.4(6)	2.7 (1.2)	NR	NR	NR	NR	0.9(0.5)	83	NR
	Placebo	84	32.6 (8.7)	67.9	5.7(6)	2.7 (1.2)	NR	NR	NR	NR	0.9(0.5)	88	
GOLDEN[96]	Fingolimod O0.5	104	39.5 (9.3)	65.4	NR(NR)	NR (NR)	NR	NR	NR	NR	NR	NR	NR
	Interferon beta 1b SC250	47	37.5 (9.3)	63.8	NR(NR)	NR (NR)	NR	NR	NR	NR	NR	NR	
IFNB Multiple Sclerosis Study Group[342]	Placebo	123	36.0 (6.7)	NR	3.9(3.3)	2.8 (1.1)	94.3	NR	NR	5.7	1.8(0.6)	0	No
	Interferon beta 1b SC250	124	35.2 (6.7)	NR	4.7(4.5)	3.0 (1.1)	93.6	NR	NR	6.4	1.7(1.1)	0	No
IMPROVE[98]	Placebo	60	35.2 (10.5)	70	NR(NR)	2.3 (NR)	NR	NR	NR	NR	NR	NR	NR
	Interferon beta 1a SC44	120	34 (7.8)	73.3	NR(NR)	2.5 (NR)	NR	NR	NR	NR	NR	NR	

Study Name	Treatment arm	N	Age (sd)	% Female	Years from diagnosis (SD)	EDSS (SD)	% White	% Black	% Asian	% Other	Annual Relapse rate (SD)	% treated	Previous treatments
INCOMIN[99]	Interferon beta 1a IM30	92	34.9 (7.9)	62	6.7(5.4)	2 (0.7)	NR	NR	NR	NR	1.4(0.5)	0	None
	Interferon beta 1b SC250	96	38.8 (7.1)	69	5.9(4.2)	2 (0.7)	NR	NR	NR	NR	1.5(0.7)	0	
Kappos 2011[100]	Placebo	54	38 (8.8)	67	2.7(0.1-19.2)	3.2 (1.4)	96	NR	NR	NR	NR	30	β interferons, glatiramer acetate, intravenous immuno-globulin, plasmapheresis, and immune-suppressive treatment
	Ocrelizumab IV600	55	35.6 (8.5)	64	3.6(0.1-16.5)	3.5 (1.5)	93	NR	NR	NR	NR	53	
	Interferon beta 1a IM30	54	38.1 (9.3)	59	3.3(0.1-20.2)	3.1 (1.5)	98	NR	NR	NR	NR	31	
Multiple Sclerosis Collaborative Research Group[105]	Interferon beta 1a IM30	158	36.7 (8.0)	75	6.6(6.2)	2.4 (0.9)	93	7	NR	0	1.2(0.6)	NR	NR
	Placebo	143	36.9 (6.8)	72	6.4(5.5)	2.3 (0.7)	92	6	NR	2	1.2(0.6)	NR	NR
OPERA I[67]	Ocrelizumab IV600	410	37.1 (9.3)	65.9	3.8(4.8)	2.9 (1.2)	NR	NR	NR	NR	1.3(0.7)	26	Interferon, Glatiramer acetate, Fingolimod, Dimethyl fumarate, Other (NR)
	Interferon beta 1a SC44	411	36.9 (9.3)	66.2	3.7(4.6)	2.8 (1.3)	NR	NR	NR	NR	1.3(0.6)	29	Interferon, Glatiramer acetate, Natalizumab, Other (NR)

Study Name	Treatment arm	N	Age (sd)	% Female	Years from diagnosis (SD)	EDSS (SD)	% White	% Black	% Asian	% Other	Annual Relapse rate (SD)	% treated	Previous treatments
OPERA II[67]	Ocrelizumab IV600	417	37.2 (9.1)	65	4.2(5)	2.8 (1.3)	NR	NR	NR	NR	1.3(0.7)	27	Interferon, Glatiramer acetate, Natalizumab, Fingolimod, Other (NR)
	Interferon beta 1a SC44	418	37.4 (9.0)	67	4.1(5.1)	2.8 (1.4)	NR	NR	NR	NR	1.3(0.7)	25	Interferon, Glatiramer acetate, Other (NR)
OPTIMUM[70]	Ofatumumab SC20	567	36.7 (8.7)	64	7.6 (6.8)	2.6 (1.2)	97	0.5	NR	2.3	1.2 (0.6)	38	Interferon beta 1a, interferon beta 1b, or glatiramer acetate
	Teriflunomide O14	566	36.8 (8.7)	66	7.7 (6.8)	2.6 (1.2)	98	0.4	NR	2.0	1.3 (0.7)	37	
PEGINTEGRITY[65]	Peginterferon beta 1a SC125	84	30 (6.5)	84.52	NR(NR)	1.1 (0.9)	NR	NR	NR	NR	NR	0	None
	Interferon beta 1a IM30	84	30.8 (7.4)	83.33	NR(NR)	1 (0.8)	NR	NR	NR	NR	NR	0	
Ponesimod Phase II study Group[101]	Ponesimod O20	116	35.5 (8.5)	67.5	NR(NR)	2.2 (1.3)	98.2	NR	NR	NR	NR	NR	NR
	Placebo	121	36.6 (8.6)	70.2	NR(NR)	2.2 (1.2)	94.2	NR	NR	NR	NR	NR	
PRISMS[102]	Placebo	187	34.6 (NR)	75	NR(NR)	2.4 (1.2)	NR	NR	NR	NR	1.5(0.7)	0	None
	Interferon beta 1a SC22	189	34.8 (NR)	67	NR(NR)	2.5 (1.2)	NR	NR	NR	NR	1.5(0.6)	0	
	Interferon beta 1a SC44	184	35.6 (NR)	66	NR(NR)	2.5 (1.3)	NR	NR	NR	NR	1.5(0.6)	0	
REGARD[103]	Interferon beta 1a SC44	386	36.7 (9.8)	69	NR(NR)	2.4 (1.3)	93%	4%	<1%	2%	NR	NR	NR
	Glatiramer acetate SC20	378	36.8 (9.5)	72	NR(NR)	2.3 (1.3)	94%	4%	<1%	2%	NR	NR	

Study Name	Treatment arm	N	Age (sd)	% Female	Years from diagnosis (SD)	EDSS (SD)	% White	% Black	% Asian	% Other	Annual Relapse rate (SD)	% treated	Previous treatments
REVEAL[78]	Natalizumab IV300	54	38.2 (8.8)	68.5	5(5.8)	NR (NR)	NR	NR	NR	NR	1.9(0.7)	48	Less than 6 months of glatiramer acetate or interferon beta
	Fingolimod O0.5	54	34.9 (8.7)	70.4	4.5(5.8)	NR (NR)	NR	NR	NR	NR	1.9(0.6)	52	
Saida 2012[104]	Placebo	57	35 (8.9)	68.4	8.2(7.3)	NR (NR)	0	0	100	0	1.7(1.6)	NR	NR
	Fingolimod O0.5	57	35 (9)	70.2	8.2(6.8)	NR (NR)	0	0	100	0	1.4(1.0)	NR	
Saida 2017[79]	Natalizumab IV300	47	37.7 (8.6)	72	5.9(5)	2.5 (1.6)	0	0	100	0	2.0(1.2)	91	IFN beta 1a, IFN beta 1b, azathioprine, fingolimod
	Placebo	47	35.1 (8.2)	68	5.1(4.9)	2.1 (1.5)	0	0	100	0	1.9(1.0)	85	
TRANSFORMS[75]	Fingolimod O0.5	431	36.7 (8.8)	65.4	7.5(6.2)	2.2 (1.3)	94.8	NR	NR	NR	1.5(1.2)	55	Interferon beta, glatiramer acetate, natalizumab
	Interferon beta 1a IM30	435	36 (8.3)	67.8	7.4(6.3)	2.2 (1.3)	93.8	NR	NR	NR	1.5(0.8)	56	

Table 49 Baseline participant details (HARRMS population)

Study Name	Treatment arm	N	Age (sd)	% Female	Years from diagnosis (SD)	EDSS (SD)	Annual Relapse rate (SD)	% treated	Previous treatments	Highly active definition
CLARITY[86]	Placebo	56	37.5 (9.3)	71.4	NR	NR	NR	100	Interferon beta 1a, interferon beta 1b, glatiramer acetate	≥ 2 relapses in previous year or ≥1 relapse and ≥1 T1 Gd+ or ≥9 T2 lesions
	Cladribine O3.5	46	36.6 (8.6)	71.7	NR	NR	NR	100		
CARE-MS II[71]	Interferon beta 1a SC44	202	35.8 (8.8)	65	4.7(2.9)	2.7 (1.2)	1.5(0.8)	100	interferon beta, glatiramer, natalizumab, immunoglobulin, azathioprine	≥ 2 relapses in previous 2 years with at ≥1 in previous year; at least one relapse while on interferon beta or glatiramer after at least 6 months of treatment
	Alemtuzumab IV12	426	34.8 (8.4)	66	4.5(2.7)	2.7 (1.3)	1.7(0.9)	100		
FREEDOMS I & II[73]	Fingolimod O0.5	249	39.3 (8.8)	76.3	6.3(5.6)	2.5 (1.3)	1.5(0.8)	100	Interferon beta 1a SC, interferon beta 1a IM, interferon beta 1b SC, glatiramer acetate, natalizumab	(1) ≥1 relapse in the previous year and either ≥1 gadolinium (Gd) enhancing T1 lesion or ≥9 T2 lesions at baseline and/or (2) as many or more relapses in the year before baseline as in the previous year
	Placebo	257	39.2 (8.4)	74.7	6.2(5.5)	2.7 (1.4)	1.6(0.9)	100		
MIST[72]	AHSCT	55	35.6 (8.4)	62	5.3 (3.7)	3.4 (1.2)	NR	100	glatiramer acetate, interferon beta 1a, interferon beta 1b, dimethyl fumarate, natalizumab, intravenous immunoglobulin, fingolimod, teriflunomide, azathioprine, methotrexate	2 or more clinical relapses or 1 relapse and MRI gadolinium-enhancing lesion(s) at a separate time within the previous 12 months despite receiving treatment with DMT
	iDMT	55	35.6 (8.2)	66	7.1 (5.1)	3.3 (1)	NR	100		
OPERA I & II combined[67]	Ocrelizumab IV600	143	NR	NR	NR	NR	NR	NR	NR	

Study Name	Treatment arm	N	Age (sd)	% Female	Years from diagnosis (SD)	EDSS (SD)	Annual Relapse rate (SD)	% treated	Previous treatments	Highly active definition
	Interferon beta 1a SC44	140	NR	NR	NR	NR	NR	NR		Treated with interferons or glatiramer acetate for at least 1 year, and • ≥1 relapse in previous year • ≥1 least one T1 Gd-enhancing lesion on brain MRI at baseline • ≥1 9 T2 hyperintense lesions on brain MRI at baseline
Saida 2017[79]	Natalizumab IV300	47	37.7 (8.6)	72	5.9(5)	2.5 (1.6)	2.0(1.2)	91	IFN beta 1a, IFN beta 1b, azathioprine, fingolimod	Not fully HARRMS; one relapse in previous year but only 88% received previous DMT
	Placebo	47	35.1 (8.2)	68	5.1(4.9)	2.1 (1.5)	1.9(1.0)	85		
TRANSFORMS[75]	Fingolimod O0.5	189	37.1 (8.8)	70.9	6.4(4.7)	2.5 (1.4)	NR	100	Beta interferon, glatiramer acetate, natilizumab	Patients who received DMT in the previous year with unchanged or increased relapse rate or ongoing severe relapses as compared with the previous year
	Interferon beta 1a IM30	191	37.1 (8.4)	67.5	6.8(6)	2.4 (1.2)	NR	100		

Appendix 4
Included study results and outcome definitions

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Table 50 Definitions of relapse, broken down into definition components, used in each of the included trials

Study Name	Symptoms	Symptom duration	Absence of	EDSS/neurological examination	Preceding stability period	Verification
ADVANCE[80]	New or recurrent neurologic symptoms	≥ 24 hours	Fever or infection	New objective neurologic findings	NR	Independent neurological evaluation committee
AFFIRM[77]	New or recurrent neurologic symptoms	≥ 24 hours	Fever or infection	New objective neurologic findings	NR	Examining neurologist
ANTELOPE[76]	New or worsening neurologic symptom	≥ 24 hours	Fever or infection	NR	≥30 days	NR
APOLITOS[69]	Symptoms (not defined)	NR	NR	EDSS increase ⩾0.5 points, or increase ⩾1 on two functional scores or ⩾2 on one	NR	NR
ASCLEPIOS I[68]	New or worsening neurologic symptom	≥ 24 hours	Fever or infection	EDSS increase ⩾0.5 points, or increase ⩾1 on two functional scores or ⩾2 on one	≥30 days	Investigator
ASSESS[81]	Symptoms (not defined)	NR	NR	EDSS increase ⩾0.5 points, or increase ⩾1 on two functional scores or ⩾2 on one	NR	Examiner ≤ 7 days of notification
BEYOND[82]	New or recurrent neurologic symptoms	≥ 24 hours	Fever or infection	Increase in EDSS or functional system scores	≥30 days	Evaluating physician
Calabrese 2012[83]	Definition not reported	NR	NR	NR	NR	NR
CAMMS223[84]	New or worsening symptoms	≥ 48 hours	Fever	New objective neurologic findings attributable to MS that	≥30 days	NR
CARE-MS I[85]	New or worsening neurologic symptom	≥ 48 hours	NR	New objective neurologic findings	≥30 days	Masked examiner
CARE-MS II[71]	New or worsening neurologic symptom attributable to MS	≥ 48 hours	Fever	Objective change on neurological examination.	≥30 days	NR
CLARITY[86]	Symptoms (not defined)	≥ 24 hours	Fever	EDSS increase ⩾0.5 points, or increase ⩾1 on two functional scores or ⩾2 on one	≥30 days	NR

Study Name	Symptoms	Symptom duration	Absence of	EDSS/neurological examination	Preceding stability period	Verification
CombiRx[87]	New or worsening neurologic symptom attributable to MS	≥ 24 hours	NR	EDSS ⩾1 on two functional scores or ⩾2 on one	≥30 days	NR
CONFIDENCE[88]	*Did not report on relapse rate*					
CONFIRM[89]	New or recurrent neurologic symptoms	≥ 24hours	Fever or infection	New objective neurologic findings	≥30 days	NR
Copolymer 1 Multiple Sclerosis Study Group[90]	New or recurrent neurologic symptoms	≥ 48 hours	Fever	EDSS increase ⩾0.5 points, or an increase or ⩾2 on one functional score	≥30 days	NR
Etemedifar 2006[91]	New or severely worsening neurologic symptom	≥ 24 hours	NR	EDSS increase ⩾1 point	NR	NR
European/Canadian glatiramer acetate study group[92]	New or recurrent neurologic symptoms	≥ 48 hours	NR	EDSS increase ⩾0.5 points, or increase ⩾1 on two functional scores or ⩾2 on one	≥30 days	Visit ≤ 7 days of notification.
EVIDENCE[93]	New or worsening neurologic symptom	≥ 24 hours	Fever	Objective change on neurological examination.	≥30 days	NR
FREEDOMS[74]	Symptoms (not defined)	NR	NR	EDSS increase ⩾0.5 points, or increase ⩾1 on two functional scores or ⩾2 on one	NR	Examining neurologist ≤ 7 days of notification
FREEDOMS II[73]	Symptoms (not defined)	NR	NR	EDSS increase ⩾0.5 points, or increase ⩾1 on two functional scores or ⩾2 on one	NR	NR
GALA[94]	New or recurrent neurologic symptoms	≥ 48 hours	NR	EDSS increase ⩾0.5 points, or increase ⩾1 on two functional scores or ⩾2 on one	≥30 days	NR
GATE[95]	New or recurrent neurologic symptoms	≥ 24 hours	Fever or infection	New objective neurologic findings	NR	NR
GOLDEN[96]	*No definition provided*					
IFNB Multiple Sclerosis Study Group[97]	New or worsening neurologic symptom attributable to MS	≥ 24 hours	Fever	New objective neurologic findings	≥30 days	NR
IMPROVE[98]	*No definition provided*					
INCOMIN[99]	New or worsening neurologic symptom	≥ 24 hours	NR	⩾1 point increase in Kurtzke's functional system scale score	≥30 days	Investigating doctor ≤ 7 days of notification

Study Name	Symptoms	Symptom duration	Absence of	EDSS/neurological examination	Preceding stability period	Verification
Kappos 2011[100]	New or worsening neurologic symptom attributable to MS	≥ 24 hours	NR	EDSS increase ⩾0.5 points, or increase ⩾1 on two functional scores or ⩾2 on one	≥30 days	NR
MIST[72]	Neurologic symptoms requiring corticosteroids	≥ 24 hours	Fever, infection, or heat intolerance	NR	NR	Investigator not masked to treatment.
Multiple Sclerosis Collaborative Research Group[105]	New or worsening neurologic symptom	≥ 48 hours	NR	EDSS increase ⩾0.5 points, or increase ⩾1 on two functional scores or ⩾2 on one	≥30 days	Study physician
OPERA I[67]	New or worsening neurologic symptom attributable to MS	≥ 24 hours	Fever, infection, injury, or adverse reactions to medications	EDSS increase ⩾0.5 points, or increase ⩾1 on two functional scores or ⩾2 on one	≥30 days	NR
OPTIMUM[70]	New, worsening or recurrent neurologic symptom	≥ 24 hours	Fever or infection	Documented increase of EDSS score or its functional system scores	≥30 days	NR
PEGINTEGRITY[65]	*No definition provided*					
Ponesimod Phase II study Group[101]	New or worsening symptoms of MS	≥ 24 hours	Fever or infection	EDSS increase ⩾0.5 points, or increase ⩾1 on two functional scores or ⩾2 on one	≥30 days	Independent neurologist ≤ 7 days of notification
PRISMS[102]	New or worsening neurologic symptom attributable to MS	≥ 24 hours	NR	NR	≥30 days	NR
REGARD[103]	New or worsening neurologic symptom	≥ 48 hours	Fever	Change in KFS score.	NR	NR
REVEAL[78]	New or recurrent neurologic symptoms	≥ 24 hours	Fever	NR	≥30 days	NR
Saida 2012[104]	New, worsening or recurrent neurologic symptom	≥ 24 hours	NR	EDSS increase ⩾0.5 points, or increase ⩾1 on two functional scores or ⩾2 on one	≥30 days	NR

Study Name	Symptoms	Symptom duration	Absence of	EDSS/neurological examination	Preceding stability period	Verification
Saida 2017[79]	New or recurrent neurologic symptoms	≥ 24 hours	Fever or infection	NR	NR	NR
TRANSFORMS[75]	New, worsening or recurrent neurologic symptom	≥ 24 hours	NR	EDSS increase ⩾0.5 points, or increase ⩾1 on two functional scores or ⩾2 on one	≥30 days	Neurologist

Table 51 Annualised relapse rate analysis details

Study Name	Analysis details	Baseline characteristics adjusted for	Other factors adjusted for
ADVANCE[80]	Negative binomial regression model	EDSS score (<4 vs ≥4); relapse rate (number of relapses in 3 years before study entry divided by 3); age (<40 vs ≥40 years)	NR
AFFIRM[77]	Poisson regression	NR	NR
ANTELOPE[76]	Analysed descriptively – summarised as A: no. relapses per patient and overall, B: duration of follow-up time per patient and overall, A/B: the ratio of relapses per patient year	NR	NR
APOLITOS[69]	Negative binomial regression models	Treatment; region; number of Gd + T1 lesions (0 or ⩾1)	Offset to adjust for time in study
ASCLEPIOS I[68]	Negative binomial-regression model	NR	Offset to adjust for time spent in trial in years
ASCLEPIOS II[68]	Negative binomial-regression model	NR	Offset to adjust for variable study duration in years
ASSESS[81]	Negative binomial-regression model	EDSS score; no. gadolinium-enhancing T1 lesions; no. relapses in previous year before enrolment	Time in study (offset variable); number of confirmed relapses for each participant (response variable)
BEYOND[82]	Hazard ratios derived from generalised linear Poisson regression	NR	NR
Calabrese 2012[83]	Only statistical analysis information provided: Between-group differences were assessed using analysis of variance, followed by the Tukey test to account for multiple comparisons. Pearson chi-square was applied to test the effect of disease-modifying on the percentage of patients that developed new cortical inflammatory lesions compared with untreated patients.	NR	NR
CAMMS223[84]	Poisson regression	NR	NR
CARE-MS I[85]	Negative binomial regression	Geographic region	Robust variance estimation used as covariate

Study Name	Analysis details	Baseline characteristics adjusted for	Other factors adjusted for
CARE-MS II[71]	NA	NA	NA
CLARITY[86]	Proportion of relapse-free patients analysed with logistic-regression model that included study-group and region effects. Odds ratio and 95% confidence intervals estimated for each study group. Groups compared with approximate chi-square test on the basis of Wald statistics.	Region; study group	NR
CombiRx[87]	Cox proportional hazards model with Anderson Gill modification to handle repeated occurrences of relapses within a participant.	Baseline covariates that differed across treatment arms	NR
CONFIDENCE[88]	NA	NA	NA
CONFIRM[89]	Negative binomial regression model	age; region; no. relapses in the 12 months before study entry	
Copolymer 1 Multiple Sclerosis Study Group[90]	ANCOVA	EDSS score; sex; duration of disease (years); prior 2-year relapse rate	
Etemedifar 2006[91]	Comparison between groups made using one-way ANOVA and repeated-measures ANOVA over time; comparisons between, before, and after 24 months of treatment within each group made using paired Student's t-test. Comparisons between proportions made by using chi-square or Fisher's exact test. Results expressed as mean (SD) and P<0.05 considered statistically significant. All statistical tests were two-sided.	NR	NR
European/Canadian glatiramer acetate study group[92]	Continuous variables analysed with two-sample two-sided t test or Mann–Whitney test	NR	NR
EVIDENCE[93]	Poisson regression model	Treatment; centre	Offset variable for time on study
FREEDOMS[74]	Negative binomial regression model	EDSS score; study group; country; no. relapses within 2 years;	NR
FREEDOMS II[73]	Negative binomial regression model		NR

Study Name	Analysis details	Baseline characteristics adjusted for	Other factors adjusted for
		EDSS score; treatment; region; no. relapses within 2 years	
GALA[94]	Negative binomial regression model	EDSS score; treatment group; no. relapses in the previous 2 years; volume of T2 lesions; status of Gd-enhancing T1 activity; country or geographical region	Offset variable for patient's exposure to treatment
GATE[95]	Not formally tested but summarized per treatment group with point estimates and 95% CIs using an appropriate covariance model	Stratification variables included as covariates	NR
GOLDEN[96]	Continuous data were summarised by mean, standard deviation (SD), median, interquartile range, minimum and maximum, and 95% confidence limits (CLs), where applicable.	NR	NR
IMPROVE[98]	Poisson regression model	Treatment	Offset variable for time on study
INCOMIN[99]	Parametric or non-parametric tests, according to distribution of variables	NR	NR
IFNB Multiple Sclerosis Study Group[97]	Treatment-group differences were analysed using ANOVA based on ranked data. In display of group exacerbation rates, 95% CI were calculated using Poisson distribution based on no. observed exacerbations in each group. Survival curves were calculated with life-table methods for length of time before onset of first and second exacerbations. Data on patients were censored at time of withdrawal. Log-rank statistic was used to test comparability of the survival curves for each group.	ANOVA accounted for treatment group; study site; treatment group by study site	NR
Kappos 2011[100]	Poisson regression	Geographical region	Offset variable for exposure time in years
MIST[72]	NA	NA	NA
Multiple Sclerosis Collaborative Research Group[105]	Divided the total number of exacerbations during the first 104 weeks by the total person-years of exposure	NR	NR

Study Name	Analysis details	Baseline characteristics adjusted for	Other factors adjusted for
OPERA I[67]	Negative binomial model	EDSS score; geographic region	NR
OPERA II[67]	Negative binomial model	EDSS score; geographic region	NR
OPTIMUM[70]	Negative binomial regression model	NR	Offset variable for log time in study in years
PEGINTEGRITY[65]	Poisson regression model with robust error variance	EDSS score; age	NR
Ponesimod Phase II study Group[101]	Rate ratio provided; time to first confirmed relapse was analysed using the Kaplan–Meier method	NR	NR
PRISMS[102]	Generalised linear model (GLM) with a log link and variance proportional to the mean	NR	NR
REGARD[103]	Poisson regression model	Treatment; centre	Offset variable for time on study
REVEAL[78]	Negative binomial regression models	NR	NR
Saida 2012[104]	Logistic regression model	EDSS score; treatment; no. relapses in two years prior to study	NR
Saida 2017[79]	Poisson regression model	NR	NR
TRANSFORMS[75]	Logistic regression model	EDSS score; country; no. relapses in previous two years	

Table 52 Estimates of ARR for each study arm in the included studies (RRMS population)

Study Name	Intervention	Follow-up (months)	N	ARR (95% CI or SD)	RR (95% CI)	ROB
ADVANCE[80]	Peginterferon beta 1a SC125	12	512	0.26 (0.21, 0.32)	0.64 (0.50, 0.83)	Low
	Placebo		500	0.4 (0.33, 0.48)	1.0	
AFFIRM[77]	Natalizumab IV300	12	627	0.27 (0.21, 0.33)	0.35 (0.26, 0.47)	Low
	Placebo		315	0.78 (0.64, 0.94)	1.0	
	Natalizumab IV300	24	627	0.23 (0.19, 0.28)	0.32 (0.24, 0.41)	
	Placebo		315	0.73 (0.62, 0.87)	1.0	
ANTELOPE[76]	Natalizumab biosimilar	6	131	0.17 (NR)	1.55 (NR)	Low
	Natalizumab IV300		133	0.11 (NR)	1.0	
APOLITOS[69]	Ofatumumab SC20	6	43	0.26 (0.11, 0.63)	0.42 (0.14, 1.25)	Some concerns
	Placebo		21	0.63 (0.28, 1.43)	1.0	
ASCLEPIOS I[68]	Ofatumumab SC20	30	454	0.11 (0.09, 0.14)	0.49 (0.37, 0.65)	Low
	Teriflunomide O14		452	0.22 (0.18, 0.26)	1.0	
ASCLEPIOS II[68]	Ofatumumab SC20	30	469	0.1 (0.08, 0.13)	0.42 (0.31, 0.56)	Low
	Teriflunomide O14		469	0.25 (0.21, 0.3)	1.0	
ASSESS[81]	Fingolimod O0.5	12	345	0.15 (0.11, 0.21)	0.59 (0.37, 0.95)	High
	Glatiramer acetate SC20		324	0.26 (0.2, 0.34)	1.0	
BEYOND[82]	Glatiramer acetate SC20	24	448	0.34 (NR)	0.94 (NR)	Some concerns
	Interferon beta 1b IM 250		897	0.36 (NR)	1.0	
Calabrese 2012[83]	Glatiramer acetate SC40	24	48	0.5 (0.39, 0.61)	1.25 (0.75, 2.07)	Some concerns
	Interferon beta 1a IM30		47	0.5 (0.33, 0.67)	1.25 (0.70, 2.22)	
	Interferon beta 1a SC44		46	0.4 (0.23, 0.57)	1.0	
CAMMS223[84]	Alemtuzumab IV12	36	112	0.11 (0.08, 0.16)	0.33 (0.2, 0.55)	High
	Interferon beta 1a SC44		111	0.36 (0.29, 0.44)	1.0	
CARE-MS I[85]	Alemtuzumab IV12	24	376	0.18 (0.13, 0.23)	0.45 (0.32, 0.63)	High
	Interferon beta 1a SC44		187	0.39 (0.29, 0.53)	1.0	
CLARITY[86]	Cladribine O3.5	24	433	0.14 (0.12, 0.17)	0.42 (0.34, 0.53)	Some concerns
	Placebo		437	0.33 (0.29, 0.38)	1.0	
CombiRx[87]	Glatiramer acetate SC20	36	259	0.23 (NR)	0.72 (NR)	Low
	Interferon beta 1a IM30		250	0.32 (NR)	1.0	
CONFIRM[89]	Glatiramer acetate SC20	24	350	0.29 (0.23, 0.35)	0.73 (0.54, 0.97)	Some concerns
	Placebo		363	0.4 (0.33, 0.49)	1.0	
Copolymer 1 Multiple Sclerosis Study Group[90]	Glatiramer acetate SC20	24	125	0.59 (NR)	0.7 (NR)	Some concerns
	Placebo		126	0.84 (NR)	1.0	
Etemedifar 2006[91]	Interferon beta 1a IM30	24	30	0.6 (NR)	2.0 (NR)	Some concerns
	Interferon beta 1b IM 250		30	0.35 (NR)	1.17 (NR)	
	Interferon beta 1a SC44		30	0.3 (NR)	1.0	
European/Canadian glatiramer acetate study group[92]	Glatiramer acetate SC20	9	119	0.81 (NR)	0.67 (NR)	Some concerns
	Placebo		120	1.21 (NR)	1.0	
EVIDENCE[93]	Interferon beta 1a IM30	16	338	0.65 (NR)	1.2(NR)	Some concerns
	Interferon beta 1a SC44		339	0.54 (NR)	1.0	
FREEDOMS[74]	Fingolimod O0.5	24	425	0.18 (0.15, 0.22)	0.45 (0.35, 0.58)	Low
	Placebo		418	0.4 (0.34, 0.47)	1.0	
FREEDOMS II[73]	Fingolimod O0.5	24	358	0.21 (0.17, 0.25)	0.52 (0.4, 0.66)	High
	Placebo		355	0.4 (0.34, 0.48)	1.0	

Study Name	Intervention	Follow-up (months)	N	ARR (95% CI or SD)	RR (95% CI)	ROB
GALA[94]	Glatiramer acetate SC40	12	943	0.33 (0.28, 0.39)	0.66 (0.54, 0.8)	Low
	Placebo		461	0.51 (0.42, 0.61)	1.0	
GATE[95]	Glatiramer acetate SC20	9	357	0.4 (0.26, 0.62)	1.05 (0.52, 2.12)	Low
	Placebo		84	0.38 (0.22, 0.66)	1.0	
GOLDEN[96]	Fingolimod O0.5	18	104	0.12 (NR)	0.31(NR)	High
	Interferon beta 1b IM 250		47	0.39 (NR)	1.0	
IFNB Multiple Sclerosis Study Group[97]	Interferon beta 1b IM 250	21.6	115	0.84 (0.72, 0.97)	0.66 (0.55, 0.80)	Some concerns
	Placebo	22.4	112	1.27 (1.12, 1.43)	1	
	Interferon beta 1b IM 250	36	124	0.84 (NR)	0.69 (NR)	
	Placebo		123	1.21 (NR)	1.0	
IMPROVE[98]	Interferon beta 1a SC44	4	120	0.14 (0.09, 0.23)	0.43 (0.23, 0.82)	Some concerns
	Placebo		60	0.33 (0.22, 0.52)	1.0	
INCOMIN[99]	Interferon beta 1b IM 250	24	96	0.5 (0.7)	0.71(NR)	High
	Interferon beta 1a IM30		92	0.7 (0.9)	1.0	
Kappos 2011[100]	Interferon beta 1a IM30	6	54	0.36 (0.22, 0.6)	0.56 (0.30, 1.06)	Low
	Ocrelizumab IV600		55	0.13 (0.03, 0.29)	0.20 (0.06, 0.67)	
	Placebo		54	0.64 (0.43, 0.94)	1.0	
Multiple Sclerosis Collaborative Research Group[105]	Interferon beta 1a IM30	24	158	0.67 (NR)	0.82(NR)	Some concerns
	Placebo	24	143	0.82 (NR)	1.0	
OPERA I[67]	Ocrelizumab IV600	24	410	0.16 (0.12, 0.2)	0.54 (0.4, 0.72)	Low
	Interferon beta 1a SC44		411	0.29 (0.24, 0.36)	1.0	
OPERA II[67]	Ocrelizumab IV600	24	417	0.16 (0.12, 0.2)	0.53 (0.4, 0.71)	Low
	Interferon beta 1a SC44		418	0.29 (0.23, 0.36)	1.0	
OPTIMUM[70]	Ponesimod O20	27	567	0.2 (0.17, 0.23)	0.69 (0.54, 0.9)	Low
	Teriflunomide O14		566	0.29 (0.25, 0.33)	1.0	
PEGINTEGRITY[65]	Interferon beta 1a IM30	24	83	0.12 (0.05, 0.27)	0.54 (0.23, 1.29)	High
	Peginterferon beta 1a SC125		84	0.06 (0.03, 0.14)	1.0	
Ponesimod Phase II study Group[101]	Ponesimod O20	6	114	0.42 (0.27, 0.65)	0.79 (0.44, 1.43)	Low
	Placebo		121	0.53 (0.36, 0.77)	1.0	
PRISMS[102]	Interferon beta 1a SC22	12	189	1.01 (0.86, 1.19)	0.68 (0.55, 0.84)	Some concerns
	Interferon beta 1a SC44		184	0.92 (0.78, 1.09)	0.62 (0.50, 0.77)	
	Placebo		187	1.49 (1.29, 1.72)	1.0	
	Interferon beta 1a SC22	24	189	0.91 (NR)	0.71 (NR)	
	Interferon beta 1a SC44		184	0.87 (NR)	0.68 (NR)	
	Placebo		187	1.28 (NR)	1.0	
REGARD[103]	Glatiramer acetate SC20	24	378	0.29 (NR)	0.97(NR)	Some concerns
	Interferon beta 1a SC44		386	0.3 (NR)	1.0	
REVEAL[78]	Natalizumab IV300	9	54	0.02 (0.01, 0.13)	0.09 (0.01, 0.72)	Some concerns
	Fingolimod O0.5		54	0.2 (0.11, 0.37)	1.0	
Saida 2012[104]	Fingolimod O0.5	6	57	0.5 (0.29, 0.87)	0.51 (0.26, 0.99)	Low
	Placebo		57	0.99 (0.67, 1.45)	1.0	
Saida 2017[79]	Natalizumab IV300	6	47	0.53 (0.29, 0.99)	0.31 (0.15, 0.62)	Low
	Placebo		47	1.73 (1.22, 2.45)	1.0	
TRANSFORMS[75]	Fingolimod O0.5	12	429	0.16 (0.12, 0.21)	0.48 (0.34, 0.70)	Low
	Interferon beta 1a IM30		431	0.33 (0.26, 0.42)	1.0	

For RR: light grey shading indicates RR estimates reported by the included studies; darker grey shading indicates studies that where RR and 95% CI were calculated from reported ARR and 95% CI for studies arms; unshaded indicates studies that did not report CIs.

Table 53 Estimates of ARR for each study arm in the included studies (HARRMS population)

Study Name	Intervention	Follow-up (months)	N	ARR (95% CI or SD)	ROB
CARE-MS II[71]	Interferon beta 1a SC44	24	202	0.52 (0.41, 0.66)	High
	Alemtuzumab IV12	24	426	0.26 (0.21, 0.33)	
CLARITY[86]	Placebo	24	56	0.44 (0.33, 0.6)	Some concerns
	Cladribine O3.5	24	46	0.25 (0.16, 0.39)	
FREEDOMS 1/II[110]	Placebo	24	257	0.46 (0.39, 0.55)	High
	Fingolimod O0.5	24	249	0.24 (0.19, 0.3)	
OPERA I/II[67]	Ocrelizumab IV600	24	143	0.099 (NR, NR)	Low
	Interferon beta 1a SC44	24	140	0.313 (NR, NR)	
Saida 2017[79]	Natalizumab IV300	6	47	0.53 (0.29, 0.99)	Low
	Placebo		47	1.73 (1.22, 2.45)	
TRANSFORMS[75]	Fingolimod O0.5	12	189	0.252 (NR, NR)	Low
	Interferon beta 1a IM30	12	191	0.506 (NR, NR)	

Disease progression

Table 54 CDP definitions and estimates of proportion of patients with CDP3 and CDP6 for each study arm in the included trials and Hazard Ratios (HR) comparing time to CDP3 and CDP6 between arms (RRMS population)

Study Name	CDP definition based on baseline EDSS scores			Intervention	Follow-up (mths)	CDP3		CDP6		ROB
	EDSS increase 0.5 point	EDSS increase 1 point	EDSS increase 1.5 pts			n/N (%)	HR (95% CI)	n/N (%)	HR (95% CI)	
ADVANCE[80]	NA	≥1	0	Peginterferon beta 1a SC125	12	31/512(6)	0.62 (0.4, 0.97)	NR/512 (NR)	0.46 (0.26, 0.81)	Low
				Placebo	12	50/500(10)	1.0	NR/500 (NR)	1.0	
AFFIRM[77]	NA	≥1	0	Natalizumab IV300	24	107/627(17)	0.58 (0.43, 0.77)	69/627 (11)	0.46 (0.33, 0.64)	Some concerns
				Placebo	24	91/315(29)	1.0	72/315 (23)	1.0	
ASCLEPIOS I[68]	>5.0	1-5	0	Ofatumumab SC20	24	45/465(10)	0.65 (0.45, 0.96)	35/465 (8)	0.61 (0.4, 0.93)	Low
				Teriflunomide O14	24	63/459(14)	1.0	53/459 (12)	1.0	
ASCLEPIOS II[68]	>5.0	1-5	0	Ofatumumab SC20	24	43/479(9)	0.66 (0.45, 0.97)	36/479 (8)	0.76 (0.49, 1.17)	Low
				Teriflunomide O14	24	62/472(13)	1.0	46/472 (10)	1.0	
BEYOND[82]	NA	All	NA	Interferon beta 1b IM 250	24	244/897(27)	NR	NR		Some concerns
				Glatiramer acetate SC20	24	92/448(21)				
CAMMS223[84]	NA	≥1	0	Alemtuzumab IV12	36	12/112(11)	0.42 (0.23, 0.77)	8/112 (7)	0.25 (0.11, 0.57)	High
				Interferon beta 1a SC44	36	16/111(14)	1.0	24/111 (22)	1.0	
CARE-MS I[85]	NA	≥1	0	Alemtuzumab IV12	24	NR		30/376 (8)	0.7 (0.4, 1.23)	High
				Interferon beta 1a SC44	24			20/187 (11)	1.0	
CLARITY[86]	NA	≥1	0	Cladribine O3.5	24	62/433(14)	0.67 (0.48, 0.93)	35/393 (8.9)	0.53 (0.36, 0.79)	Some concerns
				Placebo	24	90/437(21)	1.0	56/366 (15.3)	1.0	
CombiRx[87]	>5.0	0 to 5	NA	Interferon beta 1a IM30	36	NR		52/241 (22)	NR	Low
				Glatiramer acetate SC20	36			61/246 (25)		
CONFIRM[89]	NA	≥1	0	Glatiramer acetate SC20	24	16/350(5)	0.93 (0.63, 1.37)	NR		Some concerns
				Placebo	24	17/363(5)	1.0			

Study Name	CDP definition based on baseline EDSS scores			Intervention	Follow-up (mths)	CDP3		CDP6		ROB
	EDSS increase 0.5 point	EDSS increase 1 point	EDSS increase 1.5 pts			n/N (%)	HR (95% CI)	n/N (%)	HR (95% CI)	
Copolymer 1 Multiple Sclerosis Study Group[90]	NA	All	NA	Glatiramer acetate SC20	24	27/125(22)	NR	NR		Some concerns
				Placebo	24	31/126(25)				
EVIDENCE[93]	NA	≥1	0	Interferon beta 1a SC44	6	43/339(13)	0.87 (0.58, 1.31)	20/339 (6)	0.7 (0.39, 1.25)	Some concerns
				Interferon beta 1a IM30	6	49/338(14)	NR	30/338 (9)	1.0	
FREEDOMS[74]	>5.0	≤5	NA	Fingolimod O0.5	24	NR/425 (NR)	0.70 (0.52, 0.96)	NR/425 (NR)	0.63 (0.44, 0.90)	Low
				Placebo	24	NR/418 (NR)	1.0	NR/418 (NR)	1.0	
FREEDOMS II[73]	>5.0	≤5	NA	Fingolimod O0.5	24	91/358(25)	0.83 (0.61, 1.12)	49/358 (14)	0.72 (0.48, 1.07)	High
				Placebo	24	103/355(29)	1.0	63/355 (18)	1.0	
INCOMIN[99]	NA	All	NA	Interferon beta 1b IM 250	24	NR		13/96 (14)	0.44 (0.25, 0.8)	High
				Interferon beta 1a IM30	24			28/92 (30)	1.0	
Multiple Sclerosis Collaborative Research Group[105]	NA	All	NA	Interferon beta 1a IM30		NR		18/85 (21)	NR	Some concerns
				Placebo				29/87 (33)		
OPERA I[67]	> 5.5	≤5.5	NA	Ocrelizumab IV600	24	31/410(8)	0.57 (0.37, 0.9)	24/410 (6)	0.57 (0.34, 0.95)	Low
				Interferon beta 1a SC44	24	50/411(12)	1.0	39/411 (9)	1.0	
OPERA II[67]	> 5.5	≤5.5	NA	Ocrelizumab IV600	24	44/417(11)	0.63 (0.42, 0.92)	33/417 (8)	0.63 (0.4, 0.98)	Low
				Interferon beta 1a SC44	24	63/418(15)	1.0	48/418(11)	1.0	
OPTIMUM[70]	> 5.5	1 to 5.5	0	Ponesimod O20	27	57/567(10)	0.83 (0.58, 1.18)	46/567(8)	0.84 (0.57, 1.24)	Low
				Teriflunomide O14	27	70/566(12)	1.0	56/566(10)	1.0	
PEGINTEGRITY[65]	> 5.5	1 to 5.5	0	Peginterferon beta 1a SC125	24	1/78(1)	0.58 (0.05, 6.47)	NR		High
				Interferon beta 1a IM30	24	2/81(2)	1.0			
PRISMS[102]	> 5.5	≤5.5	NA	Interferon beta 1a SC22	12	NR/189	0.55 (0.35, 0.85)	NR		Some concerns
				Interferon beta 1a SC44	12	NR/184	0.62 (0.41, 0.95)			
				Placebo	12	NR/187	1.0			
REGARD[103]	≥5	0.5-4.5	0	Glatiramer acetate SC20	24	NR		33/378(9)	NR	Some concerns
				Interferon beta 1a SC44	24			45/386(12)		

Study Name	CDP definition based on baseline EDSS scores			Intervention	Follow-up (mths)	CDP3		CDP6		ROB
	EDSS increase 0.5 point	EDSS increase 1 point	EDSS increase 1.5 pts			n/N (%)	HR (95% CI)	n/N (%)	HR (95% CI)	
TRANSFORMS[75]	>5.0	≤5	NA	Interferon beta 1a IM30	12	34/431(8)	NR	NR		Low
				Fingolimod O0.5	12	36/429(8%)				

Table 55 CDP definitions and estimates of proportion of patients with CDP3 and CDP6 for each study arm in the included trials and Hazard Ratios (HR) comparing time to CDP3 and CDP6 between arms (HARRMS population)

Study Name	CDP definition based on baseline EDSS scores			Intervention	Follow-up (mths)	CDP3		CDP6		ROB
	EDSS increase 0.5 point	EDSS increase 1 point	EDSS increase 1.5 pts			n/N (%)	HR (95% CI)	n/N (%)	HR (95% CI)	
CARE-MS II[71]	NA	≥2	NA	Alemtuzumab IV12	24	NR		54/426(13)	0.58 (0.38, 0.87)	High
				Interferon beta 1a SC44				40/202(20)		
CLARITY[86]	NA	≥1	0	Cladribine O3.5	24	NR/46	0.25 (0.07, 0.89)	NR/46	0.20 (0.04, 0.91)	Some concerns
				Placebo		NR/56	1.0	NR/56	1.0	
FREEDOMS 1/II[110]	>5.0	≤5	NA	Fingolimod O0.5	24	NR		26/248 (10)	0.50 (0.34, 0.90)	High
				Placebo				43/257 (17)	1.0	
MIST[72]	NA	All	NA	AHSCT	34	NR		3/52 (6)	0.07 (0.02, 0.24)	High
				iDMT				34/51 (67)	1.0	
OPERA I/II[67]	> 5.5	≤5.5	NA	Ocrelizumab IV600	24	12/143 (8)	0.47 (0.23, 0.95)	10/143 (7)	0.50 (0.23, 1.09)	Low
				Interferon beta 1a SC44		22/140 (16)	1.0	17/140 (12)	1.0	

MRI outcomes

Table 56 Definitions and estimates of proportion of patients with lesions on MRI for each study arm in the included trials (RRMS population)

Study Name	Gd+ lesion definition	T2 lesions definition	Follow-up (months)	Intervention	% Gd+ lesions	% T2 lesions	ROB
AFFIRM[77]	Any Gd+ lesions	New or enlarging T2 hyperintense lesions	24	Natalizumab IV300	19/627 (3%)	267/627 (43%)	Low
				Placebo	88/315 (28%)	269/315 (85%)	
			12	Natalizumab IV300	22/627 (4%)	245/627 (39%)	
				Placebo	102/315 (32%)	243/315 (77%)	
ANTELOPE[76]	New Gd+ lesions	New or enlarging T2 lesion	6	Natalizumab biosimilar	17/126 (13%)	51/126 (40%)	Low
				Natalizumab IV300	22/127 (17%)	55/127 (43%)	
ASSESS[81]	Any Gd+ lesions	New or enlarging T2 lesions	12	Fingolimod O0.5	41/302 (14%)	147/303 (49%)	High
				Glatiramer acetate SC20	70/272 (26%)	176/272 (65%)	
CARE-MS I[85]	Any Gd+ lesions	New or enlarging T2 hyperintense lesions	24	Alemtuzumab IV12	26/366 (7%)	176/363 (48%)	High
				Interferon beta 1a SC44	34/178 (19%)	99/172 (58%)	
CLARITY[86]	Any Gd+ lesion	Active T2 lesions	24	Cladribine O3.5	54/422 (13%)	148/422 (35%)	High
				Placebo	223/424 (53%)	284/424 (67%)	
CombiRx[87]	And Gd+ lesions	NR	36	Interferon beta 1a IM30	25/187 (13%)	NR	Some concerns
				Glatiramer acetate SC20	33/215 (15%)	NR	
EVIDENCE[93]	Any Gd+ lesions	New or enlarging T2 hyperintense lesions	6	Interferon beta 1a SC44	270/325 (83%)	265/325 (82%)	Some concerns
				Interferon beta 1a IM30	287/325 (88%)	282/325 (87%)	
FREEDOMS[74]	Any Gd+ lesions	New or enlarging T2 lesion	24	Fingolimod O0.5	38/369 (10%)	183/370 (49%)	Some concerns
				Placebo	116/332 (35%)	267/339 (79%)	
FREEDOMS II[73]	Any Gd+ lesions	New hyperintense T2 lesions	24	Fingolimod O0.5	35/269 (13%)	131/264 (50%)	High
				Placebo	89/256 (35%)	186/251 (74%)	
GATE[95]	Any Gd+ lesions	New hyperintense T2 lesions	9	Glatiramer acetate SC20	193/335 (58%)	NR	Low
				Placebo	59/82 (72%)	NR	
IMPROVE[98]	New Gd+ lesions	New T2 lesions	4	Interferon beta 1a SC44	47/120 (39%)	27/120 (23%)	Some concerns
				Placebo	48/60 (80%)	30/60 (50%)	

Study Name	Gd+ lesion definition	T2 lesions definition	Follow-up (months)	Intervention	% Gd+ lesions	% T2 lesions	ROB
INCOMIN[99]	Any Gd+ lesions	New T2 lesions	12	Interferon beta 1b IM 250	7/76 (9%)	53/76 (70%)	High
				Interferon beta 1a IM30	16/73 (22%)	33/73 (45%)	
			24	Interferon beta 1b IM 250	18/76 (24%)	34/76 (45%)	
				Interferon beta 1a IM30	37/73 (51%)	54/73 (74%)	
Multiple Sclerosis Collaborative Research Group[105]	Any Gd+ lesions	NR	12	Interferon beta 1a IM30	40/134 (30%)	NR	Some concerns
				Placebo	52/123 (42%)	NR	
OPERA I[67]	Any Gd+ lesions	New or enlarging T2 lesions	24	Ocrelizumab IV600	21/410 (5%)	155/410 (38%)	Low
				Interferon beta 1a SC44	112/411 (27%)	249/411 (61%)	
OPERA II[67]	Any Gd+ lesions	New or enlarging T2 lesions	24	Ocrelizumab IV600	20/417 (5%)	153/417 (37%)	Low
				Interferon beta 1a SC44	139/418 (33%)	255/418 (61%)	
PRISMS[102]	NR	Active T2 lesions	12	Interferon beta 1a SC44	NR	66/182 (36%)	Some concerns
				Interferon beta 1a SC22	NR	94/185 (51%)	
				Placebo	NR	136/184 (74%)	
			24	Interferon beta 1a SC44	NR	126/182 (69%)	
				Interferon beta 1a SC22	NR	150/185 (81%)	
				Placebo	NR	169/184 (92%)	
REGARD[103]	Any Gd+ lesions	Active T2 lesions	24	Interferon beta 1a SC44	44/230 (19%)	137/230 (60%)	Some concerns
				Glatiramer acetate SC20	76/230 (33%)	144/230 (63%)	
REVEAL[78]	New Gd+ lesions	New/newly enlarging T2 lesions	6	Natalizumab IV300	16/47 (34%)	6/15 (40%)	Some concerns
				Fingolimod O0.5	24/45 (53%)	10/16 (63%)	
Saida 2012[104]	Any Gd+ lesions	New or enlarging T2 lesions	6	Fingolimod O0.5	11/45 (24%)	17/48 (35%)	Some concerns
				Placebo	23/50 (46%)	32/50 (64%)	
TRANSFORMS[75]	Any Gd+ lesions	New or enlarged T2-weighted hyperintense lesions	12	Fingolimod O0.5	37/374 (10%)	168/372 (45%)	Some concerns
				Interferon beta 1a IM30	68/354 (19%)	196/361 (54%)	

Table 57 Definitions and estimates of proportion of patients with lesions on MRI for each study arm in the included trials (HARRMS population)

Study Name	Gd+ lesion definition	T2 lesions definition	Follow-up (months)	Intervention	% Gd+ lesions	% T2 lesions	ROB
CARE-MS II[71]	Any Gd+ lesions	New or enlarging T2-hyperintense lesions	24	Alemtuzumab IV12	38/410 (9%)	186/403 (46%)	High
				Interferon beta 1a SC44	44/190 (23%)	127/187 (68%)	

Adverse events

Table 58 Proportion of participants reporting each of the safety outcomes of interest (RRMS population)

Study Name	Follow-up (Months)	Intervention	Number of patients experiencing each type of AE/total number of patients (% of patients)				ROB
			Any AEs	SAEs	AEs leading to treatment discontinuation	TRAE	
ADVANCE[80]	12	Placebo	417/500 (83%)	76/500 (15%)	7/500 (1%)	266/500 (53%)	Low
		Peginterferon beta 1a SC125	481/512 (94%)	5/512 (1%)	25/512 (5%)	459/512 (90%)	
AFFIRM[77]	24	Placebo	300/312 (96%)	75/312 (24%)	12/312 (4%)	NR	Low
		Natalizumab IV300	596/627 (95%)	119/627 (19%)	38/627 (6%)	NR	
ANTELOPE[76]	12	Natalizumab biosimilar	85/131 (65%)	NR	8/131 (6%)	31/131 (24%)	Low
		Natalizumab IV300	71/103 (69%)	NR	3/103 (3%)	22/103 (21%)	
APOLITOS[69]	6	Placebo	NR	0/21 (0%)	NR	17/21 (81%)	Some concerns
		Ofatumumab SC20	NR	1/43 (2%)	NR	30/43 (70%)	
ASCLEPIOS I[68]	30	Teriflunomide O14	380/462 (82%)	38/462 (8%)	24/462 (5%)	NR	Low
		Ofatumumab SC20	382/465 (82%)	48/465 (10%)	27/465 (6%)	NR	
ASCLEPIOS II[68]	30	Teriflunomide O14	408/474 (86%)	36/474 (8%)	25/474 (5%)	NR	Low
		Ofatumumab SC20	409/481 (85%)	38/481 (8%)	27/481 (6%)	NR	
ASSESS[81]	12	Fingolimod O0.5	312/345 (90%)	25/345 (7%)	32/345 (9%)	NR	High
		Glatiramer acetate SC20	283/324 (87%)	20/324 (6%)	45/324 (14%)	NR	
BEYOND[82]	Up to 42 months	Interferon beta 1b IM 250	NR	100/888 (11%)	13/888 (1%)	NR	Some concerns
		Glatiramer acetate SC20	NR	57/445 (13%)	8/445 (2%)	NR	
Calabrese 2012[83]	Did not report safety data						
CAMMS223[84]	36	Interferon beta 1a SC44	107/107 (100%)	24/107 (22%)	13/107 (12%)	NR	High
		Alemtuzumab IV12	108/108 (100%)	24/108 (22%)	2/108 (2%)	NR	
CARE-MS I[85]	24	Interferon beta 1a SC44	172/187 (92%)	27/187 (14%)	11/187 (6%)	NR	High
		Alemtuzumab IV12	361/376 (96%)	69/376 (18%)	5/376 (1%)	NR	
CLARITY[86]	24	Cladribine O3.5	347/430 (81%)	36/430 (8%)	15/430 (3%)	NR	Low

Study Name	Follow-up (Months)	Intervention	Number of patients experiencing each type of AE/total number of patients (% of patients)				ROB
			Any AEs	SAEs	AEs leading to treatment discontinuation	TRAE	
		Placebo	319/435 (73%)	28/435 (6%)	9/435 (2%)	NR	
CombiRx[87]	36	Glatiramer acetate SC20	NR	30/259 (12%)	NR	NR	Low
		Interferon beta 1a IM30	NR	38/250 (15%)	NR	NR	
CONFIDENCE[88]	6	Glatiramer acetate SC20	219/427 (51%)	8/427 (2%)	18/427 (4%)	142/427 (33%)	Some concerns
		Glatiramer acetate SC40	231/430 (54%)	13/430 (3%)	13/430 (3%)	143/430 (33%)	
CONFIRM[89]	24	Glatiramer acetate SC20	334/351 (95%)	60/351 (17%)	NR	NR	Low
		Placebo	333/363 (92%)	79/363 (22%)	NR	NR	
Copolymer 1 Multiple Sclerosis Study Group[90]	24	Placebo	NR	NR	1/126 (1%)	NR	Some concerns
		Glatiramer acetate SC20	NR	NR	5/125 (4%)	NR	
Etemedifar 2006[91]	Did not report safety data						
European/Canadian glatiramer acetate study group[92]	9	Placebo	NR	6/120 (5%)	2/120 (2%)	NR	Some concerns
		Glatiramer acetate SC20	NR	10/119 (8%)	3/119 (3%)	NR	
EVIDENCE[93]	6	Interferon beta 1a IM30	NR	18/338 (5%)	14/338 (4%)	NR	Some concerns
		Interferon beta 1a SC44	NR	21/339 (6%)	16/339 (5%)	NR	
	16	Interferon beta 1a IM30	NR	NR	18/338 (5%)	NR	
		Interferon beta 1a SC44	NR	NR	19/339 (6%)	NR	
FREEDOMS[74]	24	Placebo	387/418 (93%)	56/418 (13%)	32/418 (8%)	NR	Low
		Fingolimod O0.5	401/425 (94%)	43/425 (10%)	32/425 (8%)	NR	
FREEDOMS II[73]	24	Placebo	343/355 (97%)	45/355 (13%)	37/355 (10%)	NR	Low
		Fingolimod O0.5	350/358 (98%)	53/358 (15%)	66/358 (18%)	NR	
GALA[94]	12	Glatiramer acetate SC40	680/943 (72%)*	42/943 (4%)	29/943 (3%)	NR	Low
		Placebo	284/461 (62%)*	21/461 (5%)	6/461 (1%)	NR	
GATE[95]	9	Placebo	47/84 (56%)	2/84 (2%)	2/84 (2%)	NR	Low
		Glatiramer acetate SC20	194/357 (54%)	17/357 (5%)	4/357 (1%)	NR	
GOLDEN[96]	18	Interferon beta 1b IM 250	28/47 (60%)	1/47 (2%)	3/47 (6%)	NR	High

Study Name	Follow-up (Months)	Intervention	Number of patients experiencing each type of AE/total number of patients (% of patients)				ROB
			Any AEs	SAEs	AEs leading to treatment discontinuation	TRAE	
		Fingolimod O0.5	83/104 (80%)	9/104 (9%)	5/104 (5%)	NR	
IMPROVE[98]	4	Placebo	NR	3/60 (5%)	NR	NR	Some concerns
		Interferon beta 1a SC44	NR	4/120 (3%)	NR	NR	
INCOMIN[99]	Did not report any safety outcomes of interest; reported data for specific AEs only						
IFNB Multiple Sclerosis Study Group[97]	24	Placebo	NR	NR	1/123 (1%)	NR	Some concerns
		Interferon beta 1b IM 250	NR	NR	10/124 (8%)	NR	
Kappos 2011[100]	6	Ocrelizumab IV600	34/55 (62%)	1/55 (2%)	2/55 (4%)	17/55 (31%)	Low
		Interferon beta 1a IM30	30/54 (56%)	2/54 (4%)	1/54 (2%)	19/54 (35%)	
		Placebo	38/54 (70%)	2/54 (4%)	0/54 (0%)	25/54 (46%)	
Multiple Sclerosis Collaborative Research Group[105]	24	Placebo	NR	NR	2/143 (1%)	NR	Some concerns
		Interferon beta 1a IM30	NR	NR	7/158 (4%)	NR	
OPERA I[67]	24	Ocrelizumab IV600	327/408 (80%)	28/408 (7%)	NR	NR	Low
		Interferon beta 1a SC44	331/409 (81%)	32/409 (8%)	NR	NR	
OPERA II[67]	24	Ocrelizumab IV600	360/417 (86%)	29/417 (7%)	NR	NR	Low
		Interferon beta 1a SC44	357/417 (86%)	40/417 (10%)	NR	NR	
OPTIMUM[70]	27	Teriflunomide O14	499/566 (88%)	46/566 (8%)	34/566 (6%)	NR	Low
		Ponesimod O20	502/565 (89%)	49/565 (9%)	49/565 (9%)	NR	
PEGINTEGRITY[65]	24	Peginterferon beta 1a SC125	84/84 (100%)	2/84 (2%)	NR	63/84 (75%)	High
		Interferon beta 1a IM30	83/83 (100%)	2/83 (2%)	NR	66/83 (80%)	
Ponesimod Phase II study Group[101]	6	Placebo	90/121 (74%)	5/121 (4%)	NR	NR	Low
		Ponesimod O20	88/114 (77%)	7/114 (6%)	NR	NR	
PRISMS[102]	Did not report any safety outcomes of interest; reported data for specific AEs only						
REGARD[103]	24	Glatiramer acetate SC20	1917/375 (511%)*	27/375 (7%)	19/375 (5%)	618/375 (165%)*	Some concerns

Study Name	Follow-up (Months)	Intervention	Number of patients experiencing each type of AE/total number of patients (% of patients)				ROB
			Any AEs	SAEs	AEs leading to treatment discontinuation	TRAE	
		Interferon beta 1a SC44	1880/381 (493%)*	29/381 (8%)	23/381 (6%)	632/381 (166%)*	
REVEAL[78]	6	Natalizumab IV300	NR	0/54 (0%)	1/54 (2%)	23/54 (43%)	Some concerns
		Fingolimod O0.5	NR	2/54 (4%)	3/54 (6%)	32/54 (59%)	
Saida 2012[104]	6	Placebo	45/57 (79%)	3/57 (5%)	3/57 (5%)	NR	Low
		Fingolimod O0.5	52/57 (91%)	5/57 (9%)	6/57 (11%)	NR	
Saida 2017[79]	6	Natalizumab IV300	34/47 (72%)	7/47 (15%)	0/47 (0%)	NR	Low
		Placebo	41/47 (87%)	11/47 (23%)	1/47 (2%)	NR	
TRANSFORMS[75]	12	Interferon beta 1a IM30	395/431 (92%)	25/431 (6%)	16/431 (4%)	NR	Low
		Fingolimod O0.5	369/429 (86%)	30/429 (7%)	24/429 (6%)	NR	

*Studies reported total number of events rather than number of patients with events

Table 59 Proportion of participants reporting each of the safety outcomes of interest (HARRMS population)

Study Name	Follow-up (Months)	Intervention	Number of patients experiencing each type of AE/total number of patients (% of patients)				ROB
			Any AEs	SAEs	AEs leading to treatment discontinuation	TRAE	
CARE-MS II[71]	24	Alemtuzumab IV12	428/435 (98%)	138/435 (32%)	14/435 (3%)	NR	High
		Interferon beta 1a SC44	191/202 (95%)	77/202 (38%)	15/202 (7%)	NR	
Saida 2017[79]	6	Natalizumab IV300	34/47 (72%)	7/47 (15%)	0/47 (0%)	NR	Low
		Placebo	41/47 (87%)	11/47 (23%)	1/47 (2%)	NR	

HRQoL

Table 60 Quality of Life data (RRMS population)

Study Name	Intervention	Timepoint	EQ-5D			SF-36			Other measure reported	ROB
			N	Mean utility score (SD)	Mean VAS (SD)	Component	N	mean (SD or 95% CI)		
CLARITY[86]	Cladribine O3.5	Baseline	353	0.72 (0.20)	70.22 (19.1)	NR			NR	High
	Placebo		349	0.72 (0.19)	68.9 (21.1)					
	Cladribine O3.5	12	338	0.72 (0.22)	70.7 (18.1)					
	Placebo		318	0.70 (0.22)	67.7 (20.6)					
	Cladribine O3.5	24	345	0.73 (0.22)	71.9 (19.4)					
	Placebo		338	0.66 (0.26)	66.3 (22.6)					
FREEDOMS II[73]	Fingolimod O0.5	24	358	Mean change from baseline = –0·016 (0·20)	Mean change from baseline 0·04 (15·0)	NR			NR	High
	Placebo		355	Mean change from baseline= –0·004 (0·23); p=0.328	–0·67 (15·21); p=0·143					
ADVANCE[80]	Peginterferon beta 1a SC125	11	512	No significant change from baseline (results not reported)		MCS & PCS	512	No significant change from baseline (results not reported)	MSIS-29	Low
	Placebo	11	500			MCS	500			
CARE-MS I[85]	Alemtuzumab IV12	24	376	No difference between groups (p>0.05)		MCS & PCS	376	No difference between groups (p>0.05)	FAMS	High
	Interferon beta 1a SC44		187				187			
CONFIRM[89]	Glatiramer acetate SC20	24	338	No difference between groups (p>0.05)	No difference between groups (p>0.05)	MCS	330	Greater improvement with GA than placebo (p<0.05)	NR	Low for VAS some concerns for other QoL data
	Placebo		349				344			

Study Name	Intervention	Timepoint	EQ-5D			SF-36			Other measure reported	ROB
			N	Mean utility score (SD)	Mean VAS (SD)	Component	N	mean (SD or 95% CI)		
	Glatiramer acetate SC20		NA			PCS	330	No difference between groups (p>0.05)		
	Placebo						344			
AFFIRM[77]	Natalizumab IV300	24M	NR			MCS	536	2.00 (10.91)	NR	High
	Placebo						264	-0.53 (10.52)		
	Natalizumab IV300					PCS	536	0.67 (8.05)		
	Placebo						264	-1.34 (8.47)		
OPERA I[67]	Ocrelizumab IV600	24M	NR			PCS	410	MD change from baseline=0.69 (95% CI -0.41, 1.80); p=0.22	NR	Low
	Interferon beta 1a SC44	24M					411			
OPERA II[67]	Ocrelizumab IV600	24M	NR			PCS	417	MD change from baseline=1.16 (95% CI 0.05, 2.27); p=0.04	NR	Low
	Interferon beta 1a SC44	24M					418			

Table 61 Quality of Life data (HARRMS population)

Study Name	Intervention	Timepoint	EQ-5D			SF-36			Other QoL measures reported	ROB
			N	Mean utility score (SD)	Mean VAS (SD)	Component	N	mean (SD or 95% CI)		
CARE-MS II[71]	Alemtuzumab IV12	24	412	No difference between groups (p>0.05)	Significantly greater improvement with Alemtuzumab	MCS	410	No difference between groups (p>0.05)	FAMS	High
	Interferon beta 1a SC44		173			PCS	172	Significantly greater improvement with Alemtuzumab (p<0.01)		
MIST[72]	AHCT	12	NR			Overall	49	70 (21.3)	NR	High
	iDMT						49	46.1 (22.5); p<0.001		

Appendix 5
Additional NMA Results

ARR (RRMS population)

Table 62 Comparison of results from fixed and random effects NMA for ARR (RRMS population)

	Fixed Effects	Random effects
Intervention	**RR (95% Credible interval)**	**RR (95% Credible interval)**
Alemtuzumab IV12	0.26 (0.19, 0.36)	0.26 (0.19, 0.36)
Cladribine O3.5	0.43 (0.34, 0.53)	0.42 (0.33, 0.54)
Fingolimod O0.5	0.45 (0.39, 0.52)	0.45 (0.39, 0.53)
Glatiramer acetate SC20	0.67 (0.60, 0.75)	0.67 (0.59, 0.77)
Glatiramer acetate SC40	0.69 (0.58, 0.83)	0.70 (0.57, 0.85)
Interferon beta 1a IM30	0.83 (0.73, 0.95)	0.84 (0.72, 0.97)
Interferon beta 1a SC22	0.69 (0.56, 0.84)	0.69 (0.55, 0.86)
Interferon beta 1a SC44	0.64 (0.56, 0.73)	0.64 (0.55, 0.74)
Interferon beta 1b IM 250	0.69 (0.60, 0.80)	0.70 (0.59, 0.82)
Natalizumab biosimilar	0.47 (0.23, 0.92)	0.47 (0.24, 0.99)
Natalizumab IV300	0.31 (0.24, 0.39)	0.31 (0.23, 0.40)
Ocrelizumab IV600	0.34 (0.27, 0.43)	0.34 (0.26, 0.44)
Ofatumumab SC20	0.49 (0.27, 0.86)	0.50 (0.28, 0.90)
Peginterferon beta 1a SC125	0.63 (0.49, 0.79)	0.62 (0.48, 0.81)
Ponesimod O20	0.76 (0.46, 1.28)	0.76 (0.45, 1.30)
Teriflunomide O14	1.08 (0.62, 1.89)	1.10 (0.63, 1.92)
Tau (95% CrI)	NA	0.05 (0.002, 0.14)
Mean log odds ratio	-0.59	-0.59
Residual deviance:	49.8 (on 55 data points)	49.9 (on 55 data points)
pD	27.9	30
DIC	77.7	79.9

Note: the random effects model had good convergence (all Rhat <1.01) and so informative priors were not needed.

Chosen model: Fixed effects model

Figure 28 Model fit for ARR assessed by individual study residual deviance (fixed effects analysis; RRMS population)

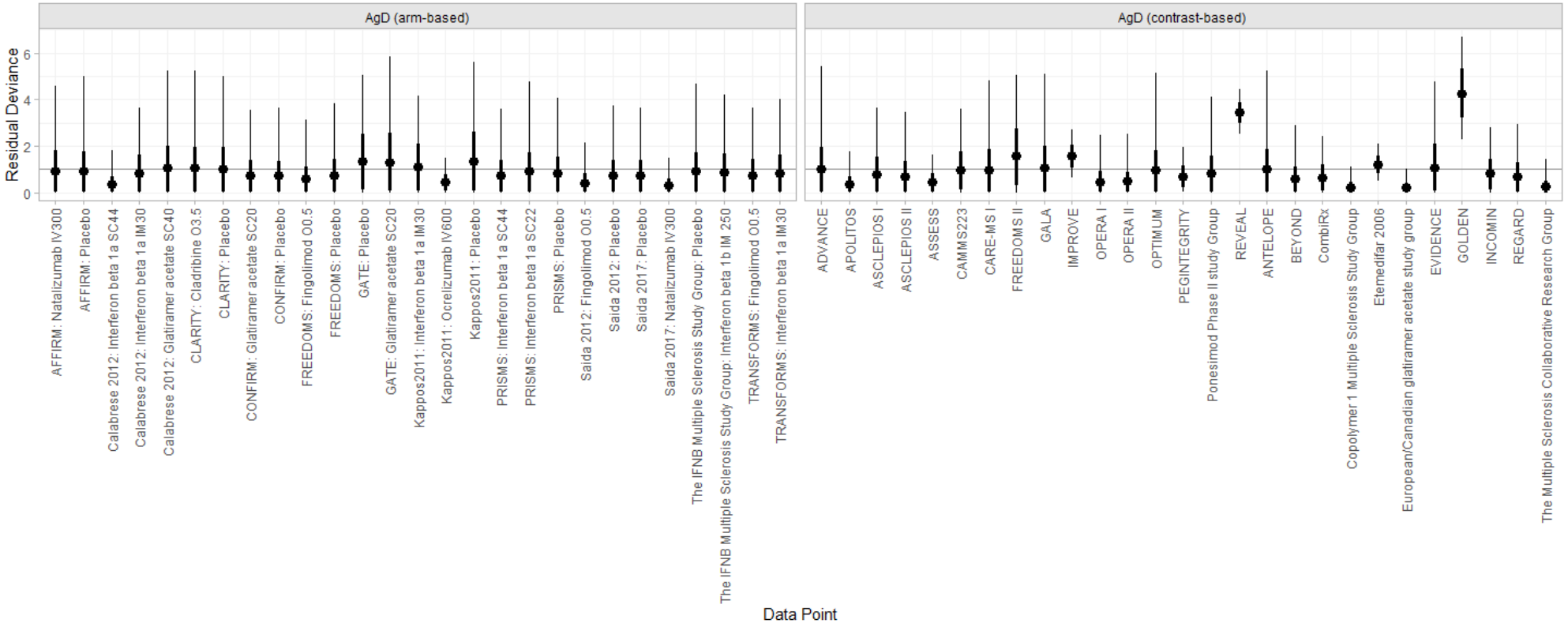

Table 63 Comparison (RR and 95% CrI) for each intervention pair for ARR (fixed effects analysis; RRMS population)

	Placebo	Alemtuzumab IV12	Cladribine O3.5	Fingolimod O0.5	Glatiramer acetate SC20	Glatiramer acetate SC40	Interferon beta 1a IM30	Interferon beta 1a SC22	Interferon beta 1a SC44	Interferon beta 1b IM 250	Natalizumab biosimilar	Natalizumab IV300	Ocrelizumab IV600	Ofatumumab SC20	Peginterferon beta 1a SC125	Ponesimod O20
Alemtuzumab IV12	0.26 (0.19, 0.36)															
Cladribine O3.5	0.43 (0.34, 0.53)	1.62 (1.10, 2.36)														
Fingolimod O0.5	0.45 (0.39, 0.52)	1.72 (1.22, 2.38)	1.06 (0.81, 1.39)													
Glatiramer acetate SC20	0.67 (0.60, 0.75)	2.56 (1.85, 3.51)	1.58 (1.22, 2.05)	1.49 (1.26, 1.77												
Glatiramer acetate SC40	0.69 (0.58, 0.83)	2.63 (1.84, 3.73)	1.63 (1.23, 2.17)	1.53 (1.22, 1.93	1.03 (0.83, 1.27											
Interferon beta 1a IM30	0.83 (0.73, 0.95)	3.17 (2.30, 4.31)	1.96 (1.51, 2.54)	1.84 (1.55, 2.21	1.24 (1.07, 1.45	1.20 (0.98, 1.48										
Interferon beta 1a SC22	0.69 (0.56, 0.84)	2.62 (1.84, 3.71)	1.62 (1.20, 2.20)	1.52 (1.20, 1.95	1.02 (0.83, 1.28	0.99 (0.76, 1.31	0.83 (0.66, 1.03									
Interferon beta 1a SC44	0.64 (0.56, 0.73)	2.44 (1.84, 3.20)	1.51 (1.16, 1.97)	1.42 (1.18, 1.72	0.95 (0.82, 1.11	0.93 (0.76, 1.14	0.77 (0.67, 0.89	0.93 (0.76, 1.14								
Interferon beta 1b IM 250	0.69 (0.60, 0.80)	2.63 (1.88, 3.65)	1.62 (1.24, 2.11)	1.53 (1.27, 1.87	1.03 (0.90, 1.19	1.00 (0.80, 1.26	0.83 (0.70, 0.98	1.01 (0.79, 1.28	1.08 (0.91, 1.29							
Natalizumab biosimilar	0.47 (0.23, 0.92)	1.80 (0.82, 3.81)	1.11 (0.53, 2.29)	1.05 (0.50, 2.07	0.70 (0.34, 1.40	0.68 (0.33, 1.38	0.57 (0.28, 1.13	0.69 (0.33, 1.40	0.74 (0.36, 1.46	0.68 (0.33, 1.36						
Natalizumab IV300	0.31 (0.24, 0.39)	1.16 (0.78, 1.70)	0.72 (0.51, 1.00)	0.68 (0.51, 0.90	0.46 (0.35, 0.60	0.44 (0.33, 0.59	0.37 (0.27, 0.48	0.45 (0.32, 0.61	0.48 (0.36, 0.63	0.44 (0.33, 0.58	0.65 (0.34, 1.26					
Ocrelizumab IV600	0.34 (0.27, 0.43)	1.29 (0.91, 1.81)	0.79 (0.57, 1.10)	0.75 (0.57, 0.99	0.50 (0.39, 0.65	0.49 (0.37, 0.65	0.41 (0.32, 0.52	0.49 (0.37, 0.66	0.53 (0.43, 0.64	0.49 (0.37, 0.64	0.71 (0.35, 1.50	1.10 (0.79, 1.53				
Ofatumumab SC20	0.49 (0.27, 0.86)	1.87 (0.99, 3.65)	1.16 (0.63, 2.15)	1.09 (0.60, 1.93	0.73 (0.40, 1.31	0.71 (0.39, 1.30	0.59 (0.33, 1.06	0.72 (0.39, 1.31	0.77 (0.43, 1.38	0.71 (0.39, 1.28	1.04 (0.43, 2.61	1.61 (0.86, 3.01	1.46 (0.79, 2.71			
Peginterferon beta 1a SC125	0.63 (0.49, 0.79)	2.38 (1.63, 3.55)	1.47 (1.05, 2.05)	1.38 (1.05, 1.82	0.93 (0.72, 1.21	0.90 (0.67, 1.22	0.75 (0.58, 0.98	0.91 (0.67, 1.23	0.98 (0.75, 1.29	0.90 (0.69, 1.18	1.32 (0.65, 2.82	2.04 (1.45, 2.87	1.85 (1.32, 2.59	1.27 (0.70, 2.39		
Ponesimod O20	0.76 (0.46, 1.28)	2.88 (1.60, 5.40)	1.78 (1.02, 3.18)	1.67 (0.98, 2.90	1.13 (0.67, 1.96	1.09 (0.64, 1.92	0.91 (0.54, 1.57	1.10 (0.64, 1.96	1.18 (0.70, 2.03	1.09 (0.64, 1.91	1.60 (0.69, 3.85	2.47 (1.42, 4.42	2.24 (1.28, 4.02	1.54 (1.10, 2.13	1.21 (0.68, 2.15	
Teriflunomide O14	1.08 (0.62, 1.89)	4.13 (2.25, 7.88)	2.55 (1.41, 4.69)	2.40 (1.35, 4.28	1.61 (0.92, 2.83	1.57 (0.89, 2.78	1.30 (0.74, 2.31	1.58 (0.88, 2.87	1.69 (0.96, 2.95	1.57 (0.87, 2.79	2.29 (0.97, 5.60	3.54 (1.94, 6.54	3.21 (1.78, 5.91	2.21 (1.79, 2.71	1.73 (0.94, 3.16	1.44 (1.11, 1.85)

Table 64 Probability that each intervention will rank in each position for ARR (fixed effects analysis; RRMS population)

Intervention	Probability of ranking position																
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Placebo	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.01	0.16	0.61	1.00
Alemtuzumab IV12	0.72	0.91	0.98	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Cladribine O3.5	0.00	0.01	0.06	0.37	0.70	0.91	0.99	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Fingolimod O0.5	0.00	0.00	0.01	0.14	0.50	0.84	0.99	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Glatiramer acetate SC20	0.00	0.00	0.00	0.00	0.00	0.00	0.02	0.11	0.26	0.45	0.68	0.85	0.96	0.99	1.00	1.00	1.00
Glatiramer acetate SC40	0.00	0.00	0.00	0.00	0.00	0.00	0.04	0.12	0.22	0.36	0.49	0.65	0.84	0.96	0.99	1.00	1.00
Interferon beta 1a IM30	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.02	0.11	0.43	0.84	1.00	1.00
Interferon beta 1a SC22	0.00	0.00	0.00	0.00	0.00	0.01	0.05	0.13	0.25	0.38	0.52	0.67	0.83	0.95	0.99	1.00	1.00
Interferon beta 1a SC44	0.00	0.00	0.00	0.00	0.00	0.02	0.11	0.31	0.55	0.75	0.89	0.96	0.99	1.00	1.00	1.00	1.00
Interferon beta 1b IM 250	0.00	0.00	0.00	0.00	0.00	0.00	0.02	0.07	0.16	0.30	0.48	0.70	0.88	0.97	1.00	1.00	1.00
Natalizumab biosimilar	0.05	0.10	0.18	0.32	0.43	0.58	0.72	0.77	0.81	0.84	0.86	0.89	0.92	0.95	0.98	0.99	1.00
Natalizumab IV300	0.17	0.65	0.93	0.99	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Ocrelizumab IV600	0.04	0.27	0.71	0.93	0.99	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Ofatumumab SC20	0.02	0.06	0.12	0.24	0.36	0.55	0.75	0.80	0.84	0.87	0.89	0.92	0.97	0.99	1.00	1.00	1.00
Peginterferon beta 1a SC125	0.00	0.00	0.00	0.00	0.01	0.06	0.24	0.48	0.62	0.71	0.79	0.87	0.94	0.98	1.00	1.00	1.00
Ponesimod O20	0.00	0.00	0.00	0.00	0.01	0.03	0.09	0.21	0.27	0.32	0.36	0.42	0.50	0.65	0.85	1.00	1.00
Teriflunomide O14	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.01	0.02	0.03	0.04	0.05	0.07	0.11	0.19	0.40	1.00

ARR (RRMS population) – sensitivity analysis restricted to studies judged at low risk of bias

Figure 29 Network plot for NMA for ARR – studies at low risk of bias

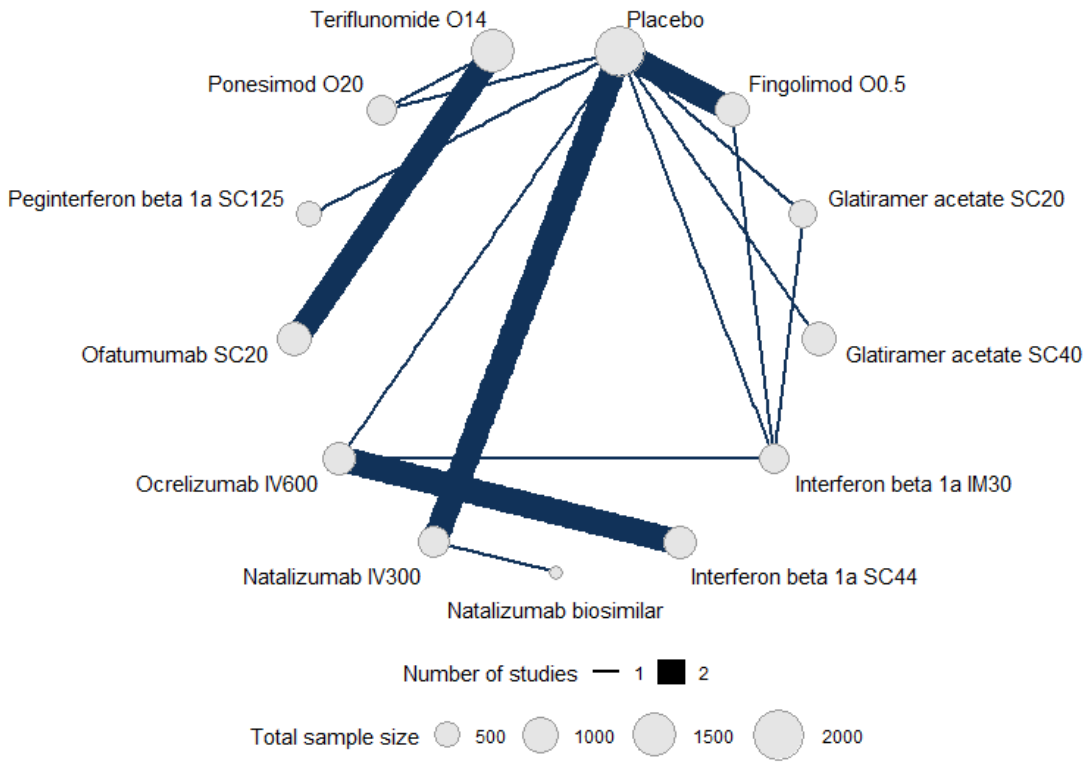

Table 65 Comparison of results from fixed and random effects NMA for ARR (RRMS population) – studies at low risk of bias

	Fixed Effects	Random effects
Intervention	**RR (95% Credible interval)**	**RR (95% Credible interval)**
Fingolimod O0.5	0.45 (0.36, 0.55)	0.45 (0.32, 0.60)
Glatiramer acetate SC20	0.70 (0.47, 1.05)	0.71 (0.45, 1.17)
Glatiramer acetate SC40	0.66 (0.54, 0.80)	0.65 (0.46, 0.95)
Interferon beta 1a IM30	0.89 (0.64, 1.23)	0.88 (0.57, 1.31)
Interferon beta 1a SC44	0.44 (0.13, 1.46)	0.45 (0.13, 1.61)
Natalizumab biosimilar	0.49 (0.25, 0.99)	0.48 (0.22, 1.09)
Natalizumab IV300	0.31 (0.25, 0.40)	0.31 (0.22, 0.45)
Ocrelizumab IV600	0.24 (0.07, 0.77)	0.24 (0.07, 0.81)
Ofatumumab SC20	0.52 (0.26, 1.01)	0.53 (0.23, 1.20)
Peginterferon beta 1a SC125	0.64 (0.50, 0.82)	0.64 (0.42, 0.92)
Ponesimod O20	0.79 (0.43, 1.41)	0.80 (0.41, 1.56)
Teriflunomide O14	1.14 (0.59, 2.15)	1.16 (0.55, 2.54)
Tau (95%CrI)	NA	0.12 (0.004, 0.40)
Mean log odds ratio	-0.58	-0.58
Residual deviance:	23.3 (on 25 data points)	23.4 (on 25 data points)
pD	19	20.4
DIC	42.2	43.9

Note: (all Rhat <1.01)

Parameters for the random effects model:

seed	437219664
prior_intercept	normal(0, scale = 5)
prior_trt	normal(0, scale = 10)
prior_het	half_normal(scale = 2)
adapt_delta	0.99

Table 66 Comparison of results from fixed and random effects NMA for ARR (RRMS population) – studies at low risk of bias

	p_rank[1]	p_rank[2]	p_rank[3]	p_rank[4]	p_rank[5]	p_rank[6]	p_rank[7]	p_rank[8]	p_rank[9]	p_rank[10]	p_rank[11]	p_rank[12]	p_rank[13]
Placebo	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.03	0.12	0.39	0.77	1.00
Fingolimod O0.5	0.00	0.06	0.27	0.61	0.89	0.98	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Glatiramer acetate SC20	0.00	0.00	0.01	0.03	0.10	0.22	0.37	0.54	0.75	0.89	0.97	0.99	1.00
Glatiramer acetate SC40	0.00	0.00	0.00	0.02	0.09	0.27	0.50	0.73	0.90	0.97	1.00	1.00	1.00
Interferon beta 1a IM30	0.00	0.00	0.00	0.00	0.00	0.01	0.02	0.07	0.21	0.45	0.71	0.91	1.00
Interferon beta 1a SC44	0.00	0.27	0.41	0.52	0.63	0.70	0.75	0.79	0.83	0.88	0.91	0.95	1.00
Natalizumab biosimilar	0.04	0.13	0.28	0.46	0.61	0.72	0.80	0.86	0.90	0.95	0.97	0.99	1.00
Natalizumab IV300	0.27	0.64	0.93	0.99	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Ocrelizumab IV600	0.66	0.79	0.87	0.91	0.94	0.96	0.97	0.98	0.99	0.99	1.00	1.00	1.00
Ofatumumab SC20	0.03	0.10	0.23	0.39	0.55	0.69	0.78	0.86	0.93	0.98	1.00	1.00	1.00
Peginterferon beta 1a SC125	0.00	0.00	0.01	0.04	0.13	0.32	0.56	0.76	0.89	0.97	1.00	1.00	1.00
Ponesimod O20	0.00	0.00	0.01	0.02	0.06	0.14	0.25	0.35	0.49	0.66	0.81	1.00	1.00
Teriflunomide O14	0.00	0.00	0.00	0.00	0.00	0.01	0.02	0.05	0.08	0.15	0.26	0.40	1.00

Disease progression: CDP3 (RRMS population)

Table 67 Comparison of results from fixed and random effects NMA for CDP3 (RRMS population)

	Fixed Effects	Random Effects
Intervention	**HR (95% Credible interval)**	**HR (95% Credible interval)**
Alemtuzumab IV12	0.26 (0.13, 0.53)	0.26 (0.11, 0.62)
Cladribine O3.5	0.67 (0.48, 0.95)	0.67 (0.42, 1.04)
Fingolimod O0.5	0.77 (0.63, 0.94)	0.77 (0.55, 1.05)
Glatiramer acetate SC20	0.91 (0.66, 1.24)	0.91 (0.60, 1.34)
Interferon beta 1a IM30	0.72 (0.49, 1.06)	0.73 (0.43, 1.21)
Interferon beta 1a SC22	0.55 (0.35, 0.85)	0.55 (0.31, 0.98)
Interferon beta 1a SC44	0.62 (0.43, 0.89)	0.63 (0.38, 1.02)
Interferon beta 1b IM 250	1.21 (0.82, 1.78)	1.20 (0.66, 2.16)
Natalizumab IV300	0.58 (0.43, 0.76)	0.58 (0.37, 0.93)
Ocrelizumab IV600	0.38 (0.24, 0.61)	0.38 (0.19, 0.70)
Peginterferon beta 1a SC125	0.61 (0.39, 0.95)	0.61 (0.33, 1.07)
Tau (95% CrI)	NA	0.14 (0.005, 0.5)
Mean log odds	-0.48	-0.48
Residual deviance	11.8 (on 16 data points)	12.8 (on 16 data points)
pD	11	12.3
DIC	22.8	25.1

Note: (all Rhat <1.01)

Parameters for the random effects model:

prior_intercept	normal(0, scale = 10)
prior_trt	normal(0, scale = 10)
prior_het	half_normal(scale = 2)
adapt_delta	0.999

Chosen model: Fixed effects model

Figure 30 Model fit for CDP3 assessed by individual study residual deviance (fixed effects analysis; RRMS population)

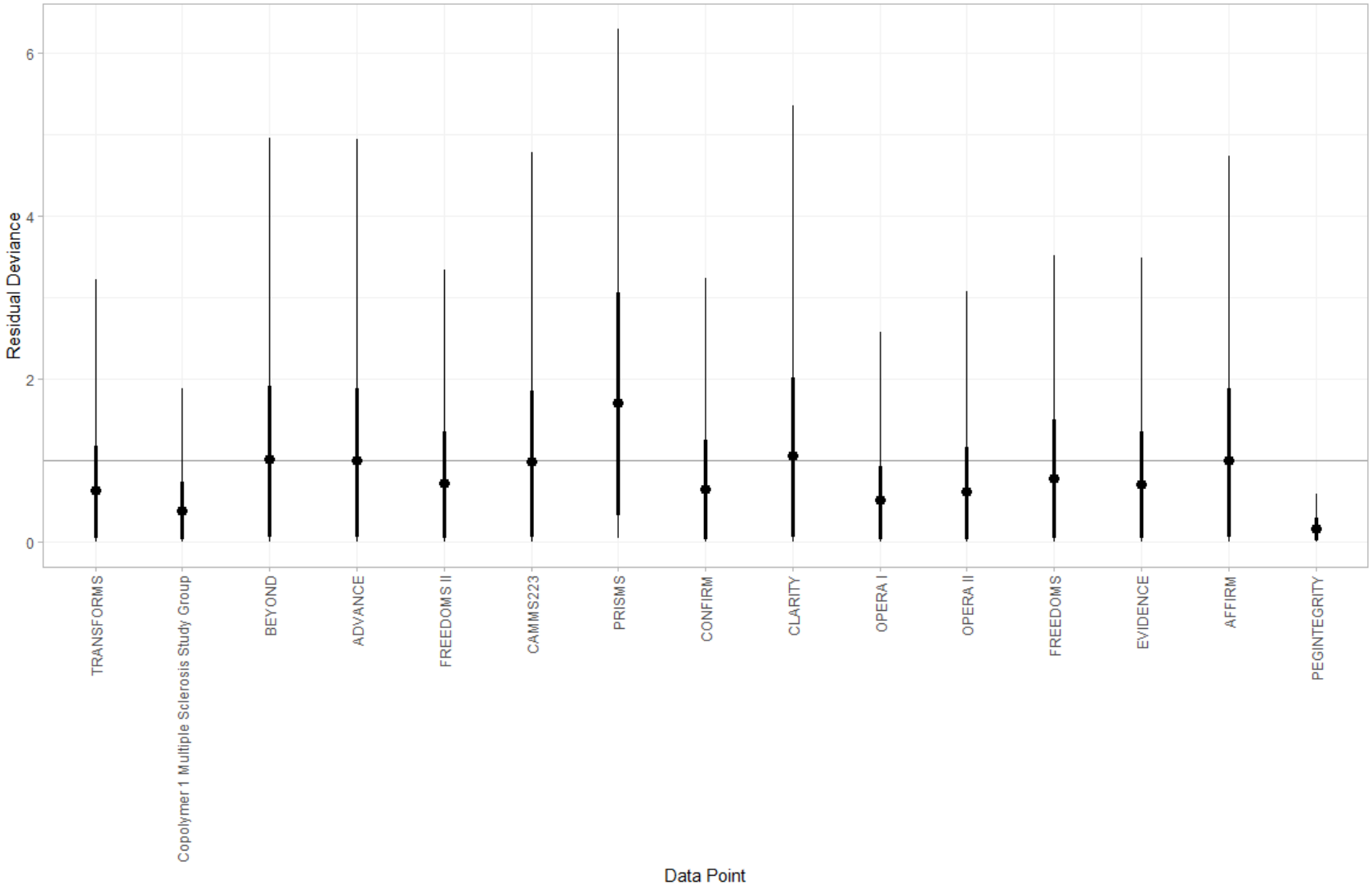

Table 68 Comparison (HR and 95% CrI) for each intervention pair for CDP3 (random effects analysis; RRMS population)

	Placebo	Alemtuzumab IV12	Cladribine O3.5	Fingolimod O0.5	Glatiramer acetate SC20	Interferon beta 1a IM30	Interferon beta 1a SC22	Interferon beta 1a SC44	Interferon beta 1b IM 250	Natalizumab IV300	Ocrelizumab IV600
Alemtuzumab IV12	0.26 (0.13, 0.53)										
Cladribine O3.5	0.67 (0.48, 0.95)	2.57 (1.19, 5.60)									
Fingolimod O0.5	0.77 (0.63, 0.94)	2.92 (1.43, 5.87)	1.14 (0.76, 1.70)								
Glatiramer acetate SC20	0.91 (0.66, 1.24)	3.48 (1.62, 7.35)	1.35 (0.85, 2.11)	1.19 (0.81, 1.72)							
Interferon beta 1a IM30	0.72 (0.49, 1.06)	2.75 (1.39, 5.44)	1.07 (0.63, 1.80)	0.94 (0.65, 1.38)	0.79 (0.49, 1.31)						
Interferon beta 1a SC22	0.55 (0.35, 0.85)	2.10 (0.92, 4.73)	0.82 (0.47, 1.42)	0.72 (0.44, 1.15)	0.60 (0.35, 1.02)	0.76 (0.42, 1.40)					
Interferon beta 1a SC44	0.62 (0.43, 0.89)	2.38 (1.31, 4.26)	0.93 (0.57, 1.53)	0.81 (0.56, 1.17)	0.68 (0.43, 1.09)	0.87 (0.62, 1.22)	1.14 (0.64, 2.02)				
Interferon beta 1b IM 250	1.21 (0.82, 1.78)	4.60 (2.05, 10.32)	1.79 (1.06, 2.99)	1.57 (1.01, 2.41)	1.32 (1.04, 1.68)	1.67 (0.95, 2.92)	2.20 (1.22, 4.00)	1.93 (1.13, 3.28)			
Natalizumab IV300	0.58 (0.43, 0.76)	2.21 (1.05, 4.76)	0.86 (0.55, 1.33)	0.76 (0.54, 1.08)	0.64 (0.42, 0.98)	0.80 (0.50, 1.31)	1.06 (0.62, 1.78)	0.93 (0.59, 1.48)	0.48 (0.30, 0.79)		
Ocrelizumab IV600	0.38 (0.24, 0.61)	1.44 (0.74, 2.81)	0.56 (0.32, 1.01)	0.49 (0.30, 0.80)	0.41 (0.24, 0.73)	0.52 (0.33, 0.81)	0.68 (0.36, 1.30)	0.60 (0.45, 0.81)	0.31 (0.17, 0.57)	0.65 (0.38, 1.13)	
Peginterferon beta 1a SC125	0.61 (0.39, 0.95)	2.34 (1.04, 5.26)	0.91 (0.53, 1.57)	0.80 (0.49, 1.30)	0.67 (0.40, 1.13)	0.85 (0.47, 1.50)	1.11 (0.60, 2.09)	0.98 (0.56, 1.69)	0.51 (0.28, 0.91)	1.06 (0.63, 1.77)	1.63 (0.84, 3.04)

Table 69 Probability that each intervention will rank in each position for CDP3 (random effects analysis; RRMS population)

	p_rank[1]	p_rank[2]	p_rank[3]	p_rank[4]	p_rank[5]	p_rank[6]	p_rank[7]	p_rank[8]	p_rank[9]	p_rank[10]	p_rank[11]	p_rank[12]
Placebo	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.02	0.32	0.84	1.00
Alemtuzumab IV12	0.83	0.96	0.98	0.99	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Cladribine O3.5	0.00	0.01	0.07	0.18	0.33	0.50	0.67	0.81	0.94	0.98	1.00	1.00
Fingolimod O0.5	0.00	0.00	0.00	0.01	0.04	0.11	0.28	0.58	0.90	0.99	1.00	1.00
Glatiramer acetate SC20	0.00	0.00	0.00	0.00	0.01	0.04	0.08	0.16	0.33	0.73	1.00	1.00
Interferon beta 1a IM30	0.00	0.00	0.03	0.09	0.19	0.33	0.50	0.70	0.86	0.95	0.98	1.00
Interferon beta 1a SC22	0.02	0.12	0.40	0.58	0.72	0.82	0.89	0.95	0.99	1.00	1.00	1.00
Interferon beta 1a SC44	0.00	0.00	0.12	0.30	0.50	0.69	0.85	0.94	0.98	1.00	1.00	1.00
Interferon beta 1b IM 250	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.01	0.02	0.06	0.19	1.00
Natalizumab IV300	0.00	0.04	0.24	0.48	0.69	0.84	0.93	0.97	1.00	1.00	1.00	1.00
Ocrelizumab IV600	0.14	0.82	0.94	0.98	0.99	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Peginterferon beta 1a SC125	0.01	0.05	0.21	0.38	0.53	0.67	0.79	0.88	0.95	0.99	1.00	1.00

Disease Progression: CDP3 (RRMS population) – sensitivity analysis restricted to studies with a follow-up ≥24 months

Figure 31 Network plot for NMA for CDP3 – studies with follow-up ≥24 months

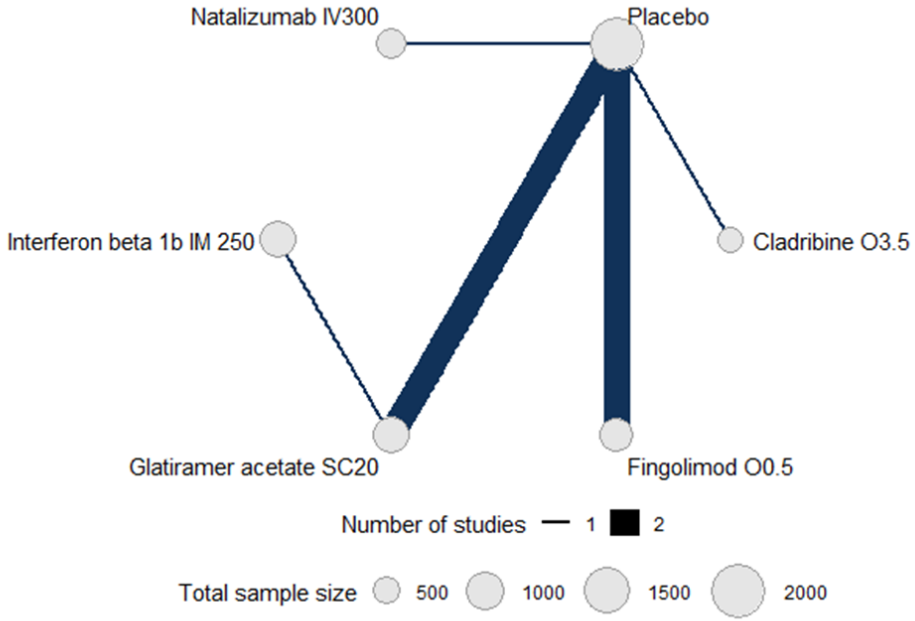

Table 70 Comparison of results from fixed and random effects, mean ranking of interventions and probability that each intervention would be ranked 1st - NMA for CDP3 – Sensitivity analysis including studies with a follow-up ≥24 months (RRMS population

	Fixed Effects	Random effects	Mean rank (95% CrI)	Pr(best) (%)
Intervention	**RR (95% Credible interval)**	**RR (95% Credible interval)**		
Cladribine O3.5	0.67 (0.48, 0.93)	0.70 (0.42, 1.31)	2.1 (1,4)	25
Fingolimod O0.5	0.76 (0.62, 0.95)	0.77 (0.52, 1.17)	2.9 (1,4)	3
Glatiramer acetate SC20	0.91 (0.67, 1.27)	0.91 (0.58, 1.42)	4.0 (2, 5)	1
Interferon beta 1b IM 250	1.21 (0.81, 1.82)	1.19 (0.61, 2.29)	5.8 (4, 6)	0
Natalizumab IV300	0.58 (0.43, 0.77)	0.61 (0.37, 1.07)	1.3 (1, 3)	71
Placebo	NA	NA	4.9 (4, 6)	0
Tau	NA	0.19 (0.01, 0.68)		
Residual deviance:	5.7 (on 7 data points)	5.8 (on 7 data points)		
pD	5.1	5.6		
DIC	10.8	11.4		

Note: (all Rhat <1.01)

Parameters for the random effects model:

prior_intercept	normal(0, scale = 10)
prior_trt	normal(0, scale = 10)
prior_het	half_normal(scale = 1)
adapt_delta	0.999

Chosen model: Fixed effects model

Disease progression: CDP6 (RRMS population)

Table 71 Comparison of results from fixed and random effects NMA for CDP6 (RRMS population)

Note: the random effects model had good convergence and so informative priors were not needed.

	Fixed effects	Random Effects
Intervention	**HR (95% Credible interval)**	**HR (95% Credible interval)**
Alemtuzumab IV12	0.34 (0.15, 0.81)	0.29 (0.06, 1.33)
Cladribine O3.5	0.53 (0.36, 0.79)	0.52 (0.18, 1.50)
Fingolimod O0.5	0.67 (0.51, 0.88)	0.67 (0.33, 1.46)
Glatiramer acetate SC20	0.63 (0.32, 1.23)	0.61 (0.16, 2.21)
Interferon beta 1a IM30	0.64 (0.36, 1.16)	0.65 (0.23, 1.89)
Interferon beta 1a SC44	0.66 (0.32, 1.40)	0.63 (0.17, 2.35)
Interferon beta 1b IM 250	0.28 (0.12, 0.64)	0.29 (0.07, 1.37)
Natalizumab IV300	0.46 (0.34, 0.64)	0.46 (0.17, 1.28)
Ocrelizumab IV600	0.40 (0.18, 0.90)	0.38 (0.08, 1.77)
Peginterferon beta 1a SC125	0.46 (0.26, 0.84)	0.46 (0.16, 1.29)
Tau (95% CrI)	NA	0.36 (0.02, 1.09)
Mean log odds	-0.71	-0.74
Residual deviance	18 (on 14 data points)	14.9 on 14 data points
pD	10.1	12.8
DIC	28.0	27.7

(all Rhat <1.01)

Parameters for the random effects model:

Seed	437219664
trt_effects	"random"
prior_intercept	normal(0, scale = 10)
prior_trt	normal(0, scale = 10)
prior_het	half_normal(scale = 2)
control	list(max_treedepth = 12),
adapt_delta	0.999

Chosen model: Fixed effects model

Figure 32 Model fit for CDP6 assessed by individual study residual deviance (random effects analysis; RRMS population)

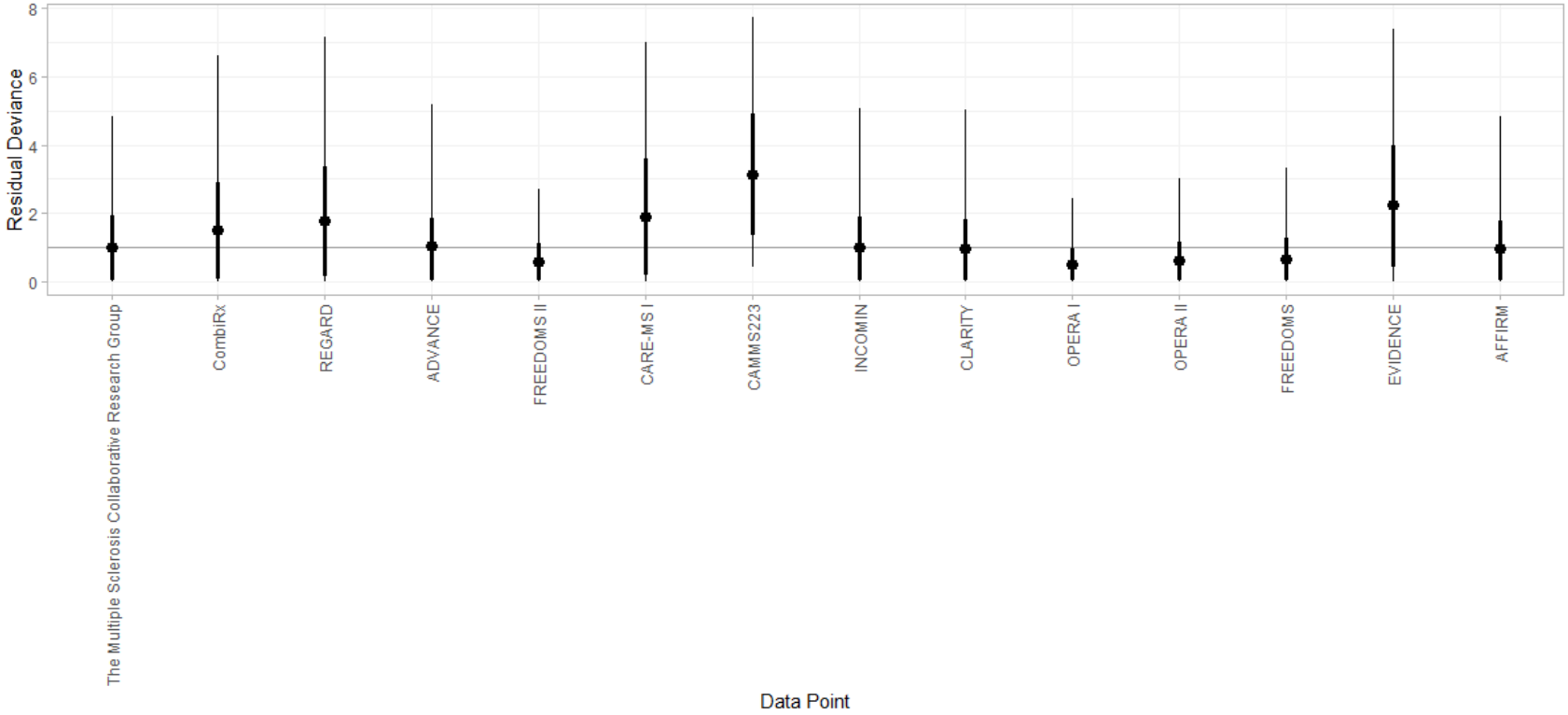

Table 72 Comparison (HR and 95% CrI) for each intervention pair for CDP6 (fixed effects analysis; RRMS population)

	Placebo	Alemtuzumab IV12	Cladribine O3.5	Fingolimod O0.5	Glatiramer acetate SC20	Interferon beta 1a IM30	Interferon beta 1a SC44	Interferon beta 1b IM 250	Natalizumab IV300	Ocrelizumab IV600
Alemtuzumab IV12	0.34 (0.15, 0.81)									
Cladribine O3.5	0.53 (0.36, 0.79)	1.58 (0.59, 3.89)								
Fingolimod O0.5	0.67 (0.51, 0.88)	1.99 (0.81, 4.78)	1.26 (0.79, 1.99)							
Glatiramer acetate SC20	0.63 (0.32, 1.23)	1.86 (1.03, 3.35)	1.18 (0.55, 2.52)	0.94 (0.45, 1.95)						
Interferon beta 1a IM30	0.64 (0.36, 1.16)	1.90 (1.04, 3.49)	1.20 (0.61, 2.46)	0.96 (0.51, 1.84)	1.02 (0.73, 1.41)					
Interferon beta 1a SC44	0.66 (0.32, 1.40)	1.97 (1.24, 3.05)	1.25 (0.56, 2.87)	0.99 (0.45, 2.19)	1.06 (0.72, 1.55)	1.04 (0.69, 1.57)				
Interferon beta 1b IM 250	0.28 (0.12, 0.64)	0.84 (0.37, 1.95)	0.53 (0.21, 1.33)	0.42 (0.18, 1.01)	0.45 (0.23, 0.87)	0.44 (0.25, 0.80)	0.43 (0.20, 0.89)			
Natalizumab IV300	0.46 (0.34, 0.64)	1.37 (0.54, 3.31)	0.87 (0.52, 1.43)	0.69 (0.45, 1.05)	0.74 (0.35, 1.55)	0.72 (0.37, 1.38)	0.70 (0.31, 1.55)	1.63 (0.68, 3.98)		
Ocrelizumab IV600	0.40 (0.18, 0.90)	1.19 (0.68, 2.10)	0.76 (0.31, 1.86)	0.60 (0.26, 1.42)	0.64 (0.39, 1.07)	0.63 (0.37, 1.08)	0.61 (0.43, 0.85)	1.42 (0.63, 3.18)	0.87 (0.37, 2.07)	
Peginterferon beta 1a SC125	0.46 (0.26, 0.84)	1.37 (0.48, 3.69)	0.87 (0.44, 1.75)	0.69 (0.37, 1.27)	0.73 (0.30, 1.79)	0.72 (0.31, 1.66)	0.69 (0.28, 1.74)	1.63 (0.58, 4.51)	1.00 (0.52, 1.91)	1.15 (0.43, 3.00)

Table 73 Probability that each intervention will rank in each position for CDP6 (fixed effects analysis; RRMS population)

	p_rank[1]	p_rank[2]	p_rank[3]	p_rank[4]	p_rank[5]	p_rank[6]	p_rank[7]	p_rank[8]	p_rank[9]	p_rank[10]	p_rank[11]
Placebo	0.00	0.00	0.00	0.00	0.00	0.00	0.01	0.05	0.09	0.17	1.00
Alemtuzumab IV12	0.26	0.57	0.75	0.84	0.91	0.96	0.99	0.99	1.00	1.00	1.00
Cladribine O3.5	0.02	0.07	0.15	0.29	0.44	0.61	0.72	0.82	0.93	1.00	1.00
Fingolimod O0.5	0.00	0.00	0.01	0.04	0.10	0.22	0.37	0.50	0.66	1.00	1.00
Glatiramer acetate SC20	0.00	0.00	0.01	0.08	0.18	0.30	0.47	0.66	0.83	0.96	1.00
Interferon beta 1a IM30	0.00	0.00	0.00	0.03	0.10	0.23	0.42	0.66	0.85	0.97	1.00
Interferon beta 1a SC44	0.00	0.00	0.00	0.06	0.14	0.24	0.36	0.52	0.70	0.90	1.00
Interferon beta 1b IM 250	0.53	0.73	0.87	0.93	0.96	0.98	0.99	1.00	1.00	1.00	1.00
Natalizumab IV300	0.04	0.16	0.31	0.52	0.70	0.81	0.89	0.96	0.99	1.00	1.00
Ocrelizumab IV600	0.06	0.25	0.55	0.69	0.81	0.90	0.96	0.98	1.00	1.00	1.00
Peginterferon beta 1a SC125	0.09	0.22	0.35	0.52	0.64	0.74	0.81	0.88	0.94	0.99	1.00

Disease Progression: CDP6 (RRMS population) – sensitivity analysis restricted to studies with a follow-up ≥24 months

Figure 33 Network plot for NMA for CDP6 – studies with follow-up ≥24 months

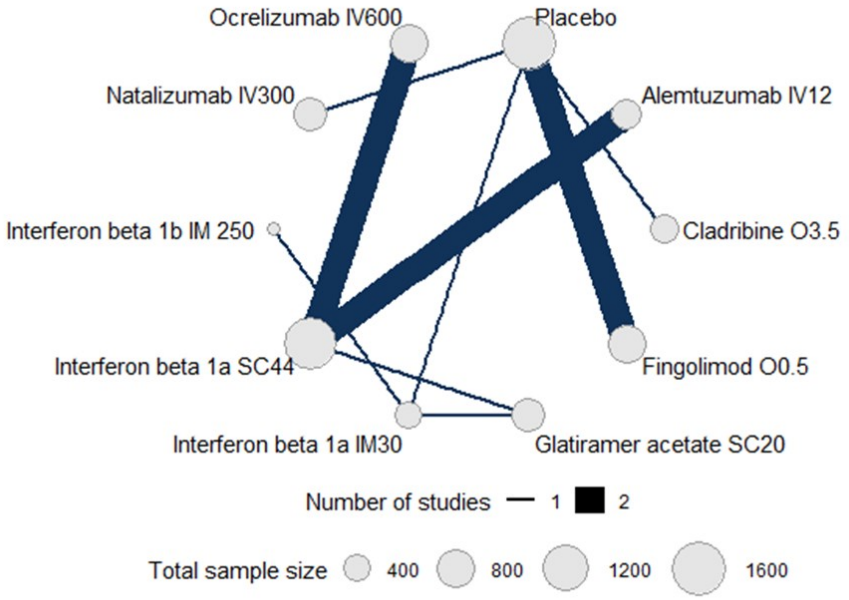

Table 74 Comparison of results from fixed and random effects, mean ranking of interventions and probability that each intervention would be ranked 1st - NMA for CDP6 – Sensitivity analysis including studies with a follow-up ≥24 months (RRMS population

	Fixed Effects	Random effects	Mean rank (95% CrI)	Pr(best) (%)
Intervention	**RR (95% Credible interval)**	**RR (95% Credible interval)**		
Alemtuzumab IV12	0.50 (0.20, 1.23)	0.44 (0.05, 2.71)	3.9 (1, 9)	9
Cladribine O3.5	0.53 (0.36, 0.78)	0.53 (0.20, 1.40)	4.3 (1, 9)	4
Fingolimod O0.5	0.67 (0.51, 0.88)	0.66 (0.33, 1.36)	6.2 (3, 9)	0
Glatiramer acetate SC20	0.74 (0.38, 1.49)	0.72 (0.15, 2.79)	7.0 (4, 9)	0
Interferon beta 1a IM30	0.64 (0.36, 1.16)	0.63 (0.22, 1.69)	5.7 (2, 9)	0
Interferon beta 1a SC44	0.99 (0.43, 2.24)	0.95 (0.15, 5.27)	9.0 (5, 10)	0
Interferon beta 1b IM 250	0.28 (0.13, 0.64)	0.28 (0.06, 1.17)	1.4 (1, 4)	74
Natalizumab IV300	0.46 (0.33, 0.64)	0.46 (0.17, 1.24)	3.2 (1, 7)	11
Ocrelizumab IV600	0.60 (0.24, 1.46)	0.57 (0.08, 3.13)	5.2 (2, 9)	2
Placebo	NA	NA	9 (6, 10)	0
Tau	NA	0.33 (0.01, 1.14)	NA	NA
Residual deviance:	13.6 (on 12 data points)	12.5 (on 12 data points)	NA	NA
pD	9.2	10.9	NA	NA
DIC	22.8	23.4	NA	NA

Note: (all Rhat <1.01)

Parameters for the random effects model:

prior_intercept	normal(0, scale = 10)
prior_trt	normal(0, scale = 10)
prior_het	half_normal(scale = 1)
adapt_delta	0.999

Chosen model: Fixed effects model

Disease Progression: CDP6 (RRMS population) – sensitivity analysis excluding INCOMIN

Figure 34 Network plot for NMA for CDP6 – excluding INCOMIN

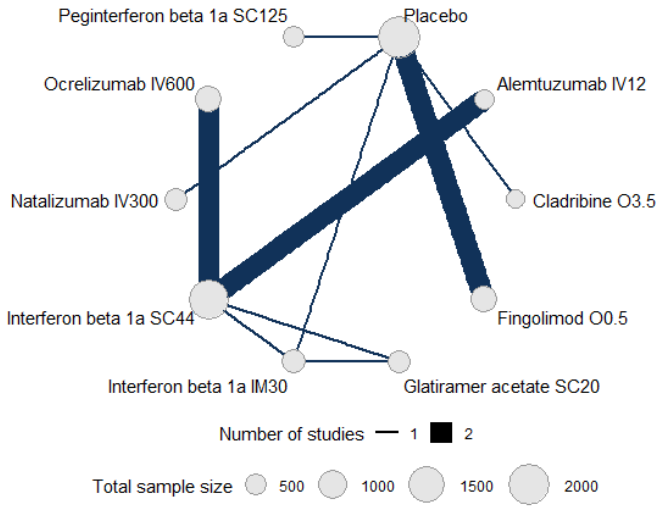

Table 75 Comparison of results from fixed and random effects, mean ranking of interventions and probability that each intervention would be ranked 1st - NMA for CDP6 – Sensitivity analysis excluding INCOMIN (RRMS population)

	Fixed Effects	Random effects	Mean rank (95% CrI)	Pr(best) (%)
Intervention	**RR (95% Credible interval)**	**RR (95% Credible interval)**		
Alemtuzumab IV12	0.33 (0.14, 0.78)	0.29 (0.05, 1.38)	2.1 (1, 6)	52
Cladribine O3.5	0.53 (0.36, 0.79)	0.53 (0.18, 1.48)	5.1 (1, 9)	4
Fingolimod O0.5	0.67 (0.51, 0.87)	0.68 (0.34, 1.46)	7.1 (3, 9)	0
Glatiramer acetate SC20	0.63 (0.32, 1.26)	0.61 (0.15, 2.53)	6.5 (3, 10)	0
Interferon beta 1a IM30	0.64 (0.36, 1.15)	0.65 (0.22, 2.04)	6.7 (3, 9)	0
Interferon beta 1a SC44	0.66 (0.33, 1.35)	0.63 (0.15, 2.46)	7.1 (3, 10)	0
Natalizumab IV300	0.46 (0.33, 0.64)	0.46 (0.17, 1.38)	3.7 (1, 8)	11
Ocrelizumab IV600	0.40 (0.18, 0.86)	0.38 (0.08, 1.78)	3.0 (1, 7)	15
Peginterferon beta 1a SC125	0.46 (0.25, 0.80)	0.47 (0.16, 1.37	4.0 (1, 9)	18
Placebo	NA	NA	9.7 (7, 10)	0
Tau	NA	0.37 (0.02, 1.17)	NA	NA
Residual deviance:	16.9 (on 13 data points)	14 (on 13 data points)	NA	NA
pD	9	12	NA	NA
DIC	25.9	26	NA	NA

Note: (all Rhat <1.01)

Parameters for the random effects model:

prior_intercept	normal(0, scale = 10)
prior_trt	normal(0, scale = 10)
prior_het	half_normal(scale = 2)
adapt_delta	0.999

Chosen model: Fixed effects model

Disease progression: CDP3 and CDP6 combined (RRMS population)

Table 76 Comparison of results from fixed and random effects NMA for CDP3 and CDP6 combined (RRMS population)

	Fixed effects	Random Effects
Intervention	**HR (95% Credible interval)**	**HR (95% Credible interval)**
Alemtuzumab IV12	0.36 (0.20, 0.62)	0.33 (0.13, 0.82)
Cladribine O3.5	0.53 (0.36, 0.78)	0.53 (0.24, 1.19)
Fingolimod O0.5	0.71 (0.56, 0.91)	0.73 (0.45, 1.21)
Glatiramer acetate SC20	0.73 (0.57, 0.93)	0.71 (0.44, 1.12)
Interferon beta 1a IM30	0.80 (0.61, 1.05)	0.81 (0.50, 1.34)
Interferon beta 1a SC22	0.55 (0.35, 0.87)	0.58 (0.26, 1.28)
Interferon beta 1a SC44	0.71 (0.53, 0.97)	0.71 (0.41, 1.23)
Interferon beta 1b IM 250	0.83 (0.60, 1.15)	0.66 (0.30, 1.31)
Natalizumab IV300	0.46 (0.33, 0.64)	0.46 (0.21, 1.03)
Ocrelizumab IV600	0.43 (0.27, 0.67)	0.43 (0.19, 0.93)
Peginterferon beta 1a SC125	0.46 (0.26, 0.81)	0.46 (0.19, 1.09)
Tau (95% CrI)	NA	0.30 (0.09, 0.66)
Mean log odds	-0.55	-0.57
Residual deviance	33.3 (on 21 data points)	21.1 (on 21 data points)
pD	11.2	17.2
DIC	44.4	38.3

Note: the random effects model had good convergence (all Rhat <1.01) and so informative priors were not needed.

Chosen model: Fixed effects model

Figure 35 Model fit for CDP3 and CDP6 combined assessed by individual study residual deviance (random effects analysis; RRMS population)

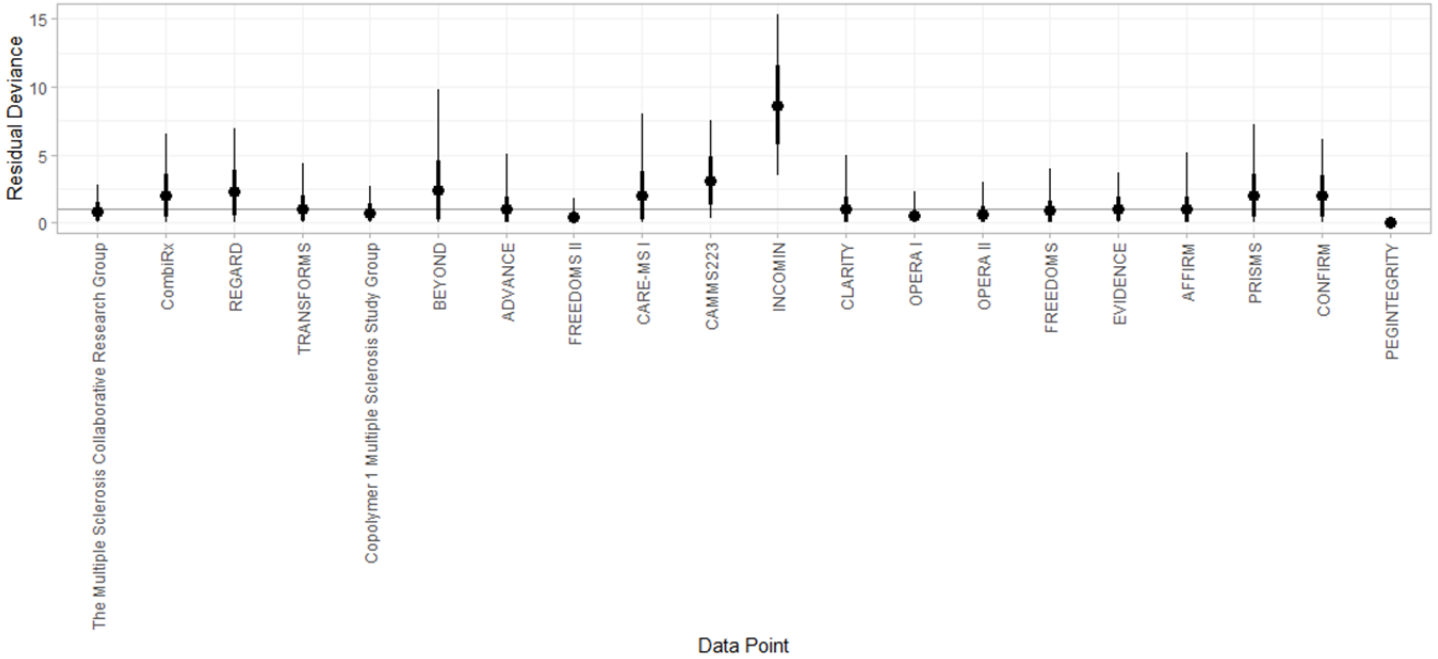

Table 77 Comparison (HR and 95% CrI) for each intervention pair for CDP3 and CDP6 combined (fixed effects analysis; RRMS population)

	Placebo	Alemtuzumab IV12	Cladribine O3.5	Fingolimod O0.5	Glatiramer acetate SC20	Interferon beta 1a IM30	Interferon beta 1a SC22	Interferon beta 1a SC44	Interferon beta 1b IM 250	Natalizumab IV300	Ocrelizumab IV600
Alemtuzumab IV12	0.36 (0.20, 0.62)										
Cladribine O3.5	0.53 (0.36, 0.78)	1.48 (0.75, 2.89)									
Fingolimod O0.5	0.71 (0.56, 0.91)	1.97 (1.13, 3.55)	1.34 (0.85, 2.10)								
Glatiramer acetate SC20	0.73 (0.57, 0.93)	2.02 (1.17, 3.59)	1.37 (0.87, 2.15)	1.02 (0.74, 1.40)							
Interferon beta 1a IM30	0.80 (0.61, 1.05)	2.23 (1.28, 3.97)	1.51 (0.94, 2.41)	1.13 (0.82, 1.55)	1.10 (0.86, 1.41)						
Interferon beta 1a SC22	0.55 (0.35, 0.87)	1.54 (0.77, 3.16)	1.04 (0.58, 1.85)	0.78 (0.46, 1.31)	0.76 (0.45, 1.29)	0.69 (0.40, 1.17)					
Interferon beta 1a SC44	0.71 (0.53, 0.97)	1.99 (1.26, 3.21)	1.35 (0.83, 2.18)	1.01 (0.71, 1.45)	0.98 (0.73, 1.34)	0.89 (0.64, 1.24)	1.29 (0.75, 2.25)				
Interferon beta 1b IM 250	0.83 (0.60, 1.15)	2.31 (1.29, 4.21)	1.57 (0.95, 2.57)	1.17 (0.79, 1.72)	1.14 (0.90, 1.43)	1.04 (0.76, 1.41)	1.51 (0.86, 2.65)	1.16 (0.80, 1.69)			
Natalizumab IV300	0.46 (0.33, 0.64)	1.28 (0.69, 2.44)	0.87 (0.52, 1.44)	0.65 (0.42, 0.98)	0.63 (0.42, 0.96)	0.57 (0.37, 0.89)	0.83 (0.48, 1.45)	0.64 (0.41, 1.00)	0.55 (0.35, 0.89)		
Ocrelizumab IV600	0.43 (0.27, 0.67)	1.20 (0.67, 2.13)	0.81 (0.44, 1.46)	0.61 (0.37, 0.99)	0.59 (0.38, 0.93)	0.54 (0.33, 0.85)	0.78 (0.42, 1.47)	0.60 (0.43, 0.84)	0.52 (0.31, 0.85)	0.94 (0.54, 1.64)	
Peginterferon beta 1a SC125	0.46 (0.26, 0.81)	1.29 (0.59, 2.84)	0.87 (0.45, 1.71)	0.65 (0.36, 1.20)	0.64 (0.34, 1.17)	0.58 (0.31, 1.08)	0.84 (0.40, 1.71)	0.65 (0.33, 1.23)	0.56 (0.29, 1.08)	1.01 (0.53, 1.94)	1.07 (0.51, 2.23)

Table 78 Probability that each intervention will rank in each position for CDP3 and CDP6 combined (fixed effects analysis; RRMS population)

	p_rank[1]	p_rank[2]	p_rank[3]	p_rank[4]	p_rank[5]	p_rank[6]	p_rank[7]	p_rank[8]	p_rank[9]	p_rank[10]	p_rank[11]	p_rank[12]
Placebo	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.03	0.19	1.00
Alemtuzumab IV12	0.51	0.73	0.85	0.92	0.97	0.99	1.00	1.00	1.00	1.00	1.00	1.00
Cladribine O3.5	0.04	0.11	0.24	0.44	0.67	0.85	0.92	0.95	0.98	0.99	1.00	1.00
Fingolimod O0.5	0.00	0.00	0.00	0.01	0.06	0.19	0.44	0.64	0.80	0.92	1.00	1.00
Glatiramer acetate SC20	0.00	0.00	0.00	0.01	0.04	0.12	0.31	0.59	0.85	0.98	1.00	1.00
Interferon beta 1a IM30	0.00	0.00	0.00	0.00	0.01	0.03	0.09	0.21	0.40	0.69	0.96	1.00
Interferon beta 1a SC22	0.03	0.11	0.22	0.37	0.57	0.76	0.85	0.90	0.93	0.97	0.99	1.00
Interferon beta 1a SC44	0.00	0.00	0.00	0.01	0.06	0.19	0.41	0.62	0.78	0.91	0.99	1.00
Interferon beta 1b IM 250	0.00	0.00	0.00	0.00	0.01	0.04	0.08	0.16	0.29	0.54	0.87	1.00
Natalizumab IV300	0.10	0.27	0.53	0.77	0.91	0.98	0.99	0.99	1.00	1.00	1.00	1.00
Ocrelizumab IV600	0.15	0.44	0.65	0.80	0.91	0.98	0.99	1.00	1.00	1.00	1.00	1.00
Peginterferon beta 1a SC125	0.17	0.34	0.51	0.66	0.79	0.88	0.92	0.95	0.97	0.98	1.00	1.00

MRI Gd+ lesions (RRMS population)

Table 79 Comparison of results from fixed and random effects NMA for MRI Gd+ lesions (RRMS population)

	Fixed effects	Random Effects
Intervention	**HR (95% Credible interval)**	**HR (95% Credible interval)**
Alemtuzumab IV12	0.20 (0.11, 0.35)	0.19 (0.10, 0.37)
Cladribine O3.5	0.24 (0.18, 0.33)	0.24 (0.16, 0.37)
Fingolimod O0.5	0.33 (0.27, 0.40)	0.33 (0.26, 0.42)
Glatiramer acetate SC20	0.77 (0.62, 0.95)	0.76 (0.58, 0.99)
Interferon beta 1a IM30	0.60 (0.47, 0.75)	0.61 (0.46, 0.81)
Interferon beta 1a SC44	0.53 (0.42, 0.67)	0.52 (0.38, 0.69)
Interferon beta 1b IM 250	0.28 (0.15, 0.51)	0.28 (0.15, 0.56)
Natalizumab biosimilar	0.11 (0.05, 0.22)	0.11 (0.05, 0.25)
Natalizumab IV300	0.14 (0.09, 0.21)	0.14 (0.09, 0.22)
Ocrelizumab IV600	0.09 (0.06, 0.13	0.09 (0.05, 0.14)
Tau (95%CrI)	NA	0.11 (0.006, 0.32)
Mean log odds ratio	-1.35	-1.35
Residual deviance	17.8 (on 19 data points)	16.5 (on 19 data points)
pD	10.2	12
DIC	27.9	28.5

Note: the random effects model had good convergence (all Rhat <1.01) and so informative priors were not needed.

Chosen model: Fixed effects model

Figure 36 Model fit for MRI Gd+ lesions combined assessed by individual study residual deviance (fixed effects analysis; RRMS population)

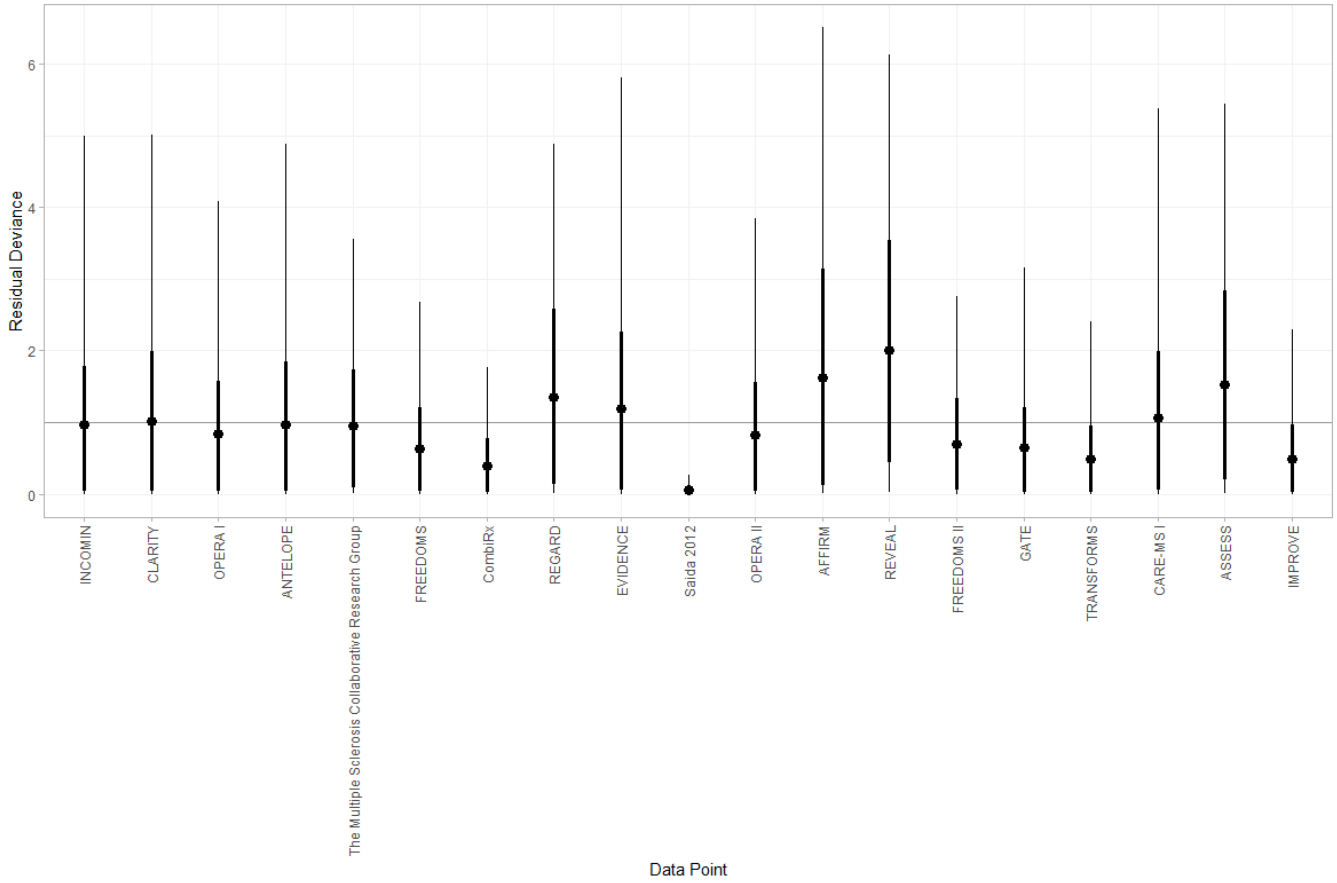

Table 80 Comparison (HR and 95% CrI) for each intervention pair for MRI Gd+ lesions (fixed effects analysis; RRMS population)

	Placebo	Alemtuzumab IV12	Cladribine O3.5	Fingolimod O0.5	Glatiramer acetate SC20	Interferon beta 1a IM30	Interferon beta 1a SC44	Interferon beta 1b IM 250	Natalizumab biosimilar	Natalizumab IV300
Alemtuzumab IV12	0.20 (0.11, 0.35)									
Cladribine O3.5	0.24 (0.18, 0.33)	1.23 (0.64, 2.39)								
Fingolimod O0.5	0.33 (0.27, 0.40)	1.66 (0.94, 2.99)	1.35 (0.94, 1.94)							
Glatiramer acetate SC20	0.77 (0.62, 0.95)	3.87 (2.16, 7.01)	3.14 (2.14, 4.56)	2.33 (1.83, 3.00)						
Interferon beta 1a IM30	0.60 (0.47, 0.75)	3.01 (1.76, 5.25)	2.45 (1.68, 3.60)	1.82 (1.42, 2.34)	0.78 (0.61, 0.99)					
Interferon beta 1a SC44	0.53 (0.42, 0.67)	2.69 (1.61, 4.66)	2.19 (1.51, 3.19)	1.62 (1.25, 2.11)	0.70 (0.55, 0.88)	0.89 (0.77, 1.04)				
Interferon beta 1b IM 250	0.28 (0.15, 0.51)	1.41 (0.65, 3.08)	1.15 (0.59, 2.20)	0.85 (0.47, 1.56)	0.36 (0.20, 0.67)	0.47 (0.27, 0.81)	0.52 (0.30, 0.93)			
Natalizumab biosimilar	0.11 (0.05, 0.22)	0.55 (0.22, 1.36)	0.44 (0.20, 0.98)	0.33 (0.16, 0.69)	0.14 (0.07, 0.30)	0.18 (0.09, 0.39)	0.20 (0.10, 0.43)	0.39 (0.15, 0.98)		
Natalizumab IV300	0.14 (0.09, 0.21)	0.70 (0.35, 1.44)	0.57 (0.35, 0.97)	0.42 (0.29, 0.64)	0.18 (0.12, 0.28)	0.23 (0.15, 0.36)	0.26 (0.17, 0.41)	0.50 (0.25, 1.00)	1.29 (0.69, 2.37)	
Ocrelizumab IV600	0.09 (0.06, 0.13)	0.44 (0.24, 0.83)	0.36 (0.22, 0.59)	0.27 (0.17, 0.41)	0.11 (0.08, 0.17)	0.15 (0.10, 0.21)	0.16 (0.12, 0.23)	0.31 (0.16, 0.62)	0.81 (0.35, 1.85)	0.63 (0.36, 1.10)

Table 81 Probability that each intervention will rank in each position for MRI Gd+ lesions (fixed effects analysis; RRMS population)

	p_rank[1]	p_rank[2]	p_rank[3]	p_rank[4]	p_rank[5]	p_rank[6]	p_rank[7]	p_rank[8]	p_rank[9]	p_rank[10]	p_rank[11]
Placebo	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.01	1.00
Alemtuzumab IV12	0.00	0.06	0.19	0.66	0.87	0.97	1.00	1.00	1.00	1.00	1.00
Cladribine O3.5	0.00	0.00	0.02	0.22	0.69	0.96	1.00	1.00	1.00	1.00	1.00
Fingolimod O0.5	0.00	0.00	0.00	0.00	0.04	0.36	1.00	1.00	1.00	1.00	1.00
Glatiramer acetate SC20	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.02	0.99	1.00
Interferon beta 1a IM30	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.08	0.98	1.00	1.00
Interferon beta 1a SC44	0.00	0.00	0.00	0.00	0.00	0.00	0.01	0.92	1.00	1.00	1.00
Interferon beta 1b IM 250	0.00	0.01	0.03	0.15	0.40	0.71	0.99	0.99	1.00	1.00	1.00
Natalizumab biosimilar	0.30	0.76	0.92	0.98	0.99	1.00	1.00	1.00	1.00	1.00	1.00
Natalizumab IV300	0.01	0.22	0.85	0.99	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Ocrelizumab IV600	0.68	0.95	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00

MRI T2 weighted lesions (RRMS population)

Table 82 Comparison of results from fixed and random effects NMA for MRI T2 weighted lesions (RRMS population)

	Fixed effects	Random Effects
Intervention	**HR (95% Credible interval)**	**HR (95% Credible interval)**
Alemtuzumab IV12	0.61 (0.45, 0.81)	0.60 (0.41, 0.86)
Cladribine O3.5	0.52 (0.43, 0.64)	0.52 (0.39, 0.69)
Fingolimod O0.5	0.63 (0.55, 0.72)	0.63 (0.53, 0.73)
Glatiramer acetate SC20	0.80 (0.66, 0.98)	0.79 (0.61, 1.01)
Interferon beta 1a IM30	0.77 (0.64, 0.92)	0.75 (0.59, 0.95)
Interferon beta 1a SC22	0.88 (0.71, 1.10)	0.87 (0.66, 1.15)
Interferon beta 1a SC44	0.72 (0.61, 0.85)	0.71 (0.57, 0.86)
Interferon beta 1b IM 250	0.46 (0.29, 0.73)	0.46 (0.27, 0.76)
Natalizumab biosimilar	0.46 (0.30, 0.70)	0.46 (0.28, 0.74)
Natalizumab IV300	0.50 (0.42, 0.59)	0.49 (0.38, 0.62)
Ocrelizumab IV600	0.44 (0.36, 0.55)	0.43 (0.32, 0.57)
Tau	NA	0.07 (0.002, 0.25)
Mean log odds ratio	-0.51	-0.52
Residual deviance	15.4 (on 18 data points)	15.6 (on 18 data points)
pD	11	12.3
DIC	26.4	27.9

(all Rhat <1.01)

RE parameters:

seed	437219664
prior_intercept	normal(0, scale = 10)
prior_trt	normal(0, scale = 10)
prior_het	half_normal(scale = 2)
adapt_delta	0.999

Chosen model: Fixed effects model

Figure 37 Model fit for MRI T2 weighted lesions assessed by individual study residual deviance (fixed effects analysis; RRMS population)

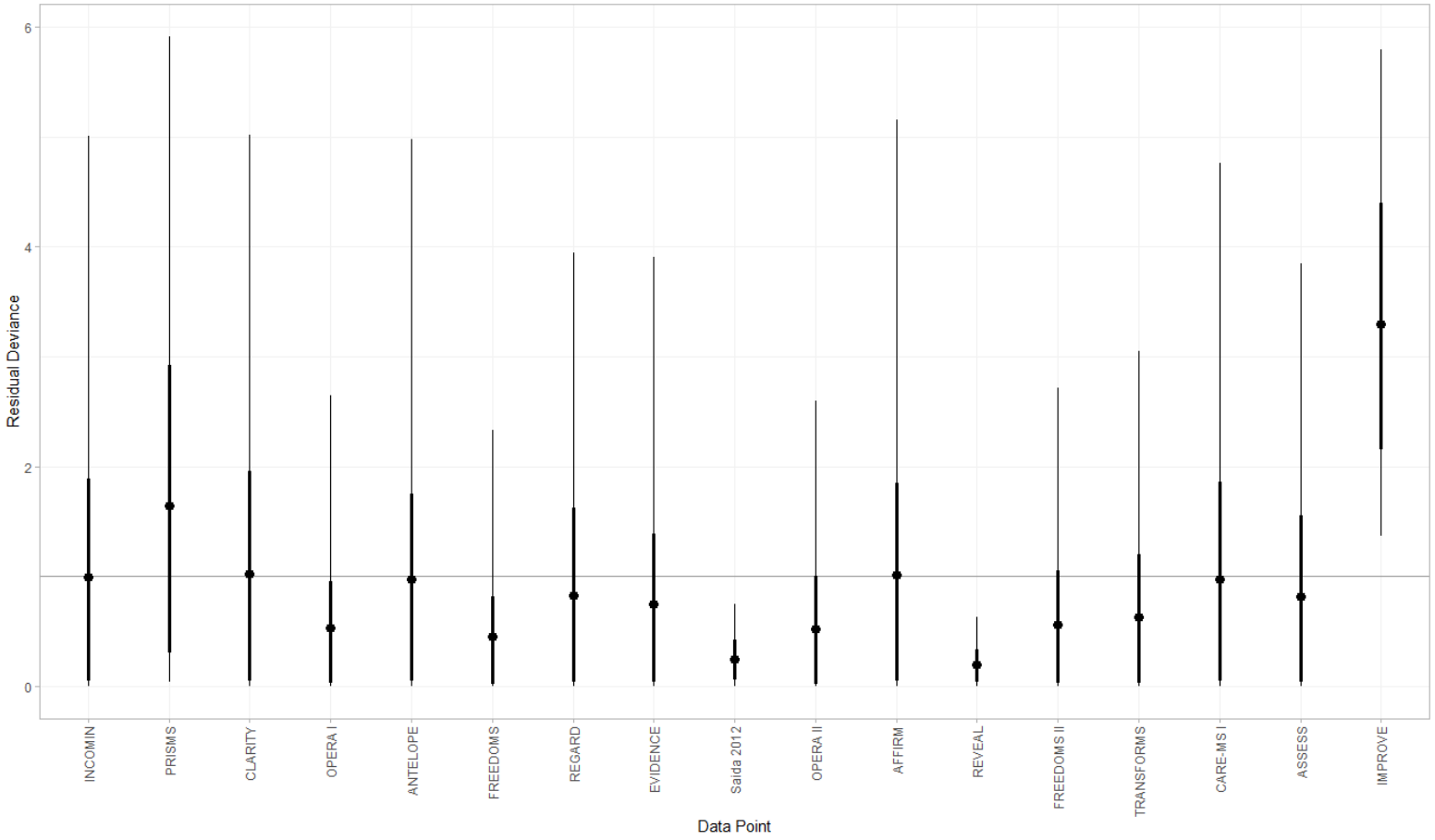

Table 83 Comparison (HR and 95% CrI) for each intervention pair for MRI T2 weighted lesions (fixed effects analysis; RRMS population)

	Placebo	Alemtuzumab IV12	Cladribine O3.5	Fingolimod O0.5	Glatiramer acetate SC20	Interferon beta 1a IM30	Interferon beta 1a SC22	Interferon beta 1a SC44	Interferon beta 1b IM 250	Natalizumab biosimilar	Natalizumab IV300
Alemtuzumab IV12	0.61 (0.45, 0.81)										
Cladribine O3.5	0.52 (0.43, 0.64)	0.86 (0.61, 1.23)									
Fingolimod O0.5	0.63 (0.55, 0.72)	1.04 (0.78, 1.40)	1.21 (0.96, 1.53)								
Glatiramer acetate SC20	0.80 (0.66, 0.98)	1.32 (0.99, 1.80)	1.53 (1.16, 2.03)	1.27 (1.07, 1.52)							
Interferon beta 1a IM30	0.77 (0.64, 0.92)	1.26 (0.95, 1.68)	1.46 (1.12, 1.92)	1.21 (1.03, 1.43)	0.95 (0.78, 1.17)						
Interferon beta 1a SC22	0.88 (0.71, 1.10)	1.45 (1.01, 2.09)	1.69 (1.25, 2.29)	1.40 (1.09, 1.79)	1.10 (0.83, 1.47)	1.15 (0.87, 1.52)					
Interferon beta 1a SC44	0.72 (0.61, 0.85)	1.19 (0.94, 1.50)	1.38 (1.06, 1.79)	1.14 (0.97, 1.34)	0.90 (0.75, 1.08)	0.94 (0.82, 1.09)	0.82 (0.62, 1.08)				
Interferon beta 1b IM 250	0.46 (0.29, 0.73)	0.76 (0.46, 1.29)	0.88 (0.52, 1.45)	0.73 (0.46, 1.15)	0.58 (0.36, 0.92)	0.60 (0.39, 0.92)	0.52 (0.31, 0.87)	0.64 (0.41, 1.00)			
Natalizumab biosimilar	0.46 (0.30, 0.70)	0.76 (0.46, 1.27)	0.88 (0.55, 1.41)	0.73 (0.47, 1.12)	0.57 (0.36, 0.90)	0.60 (0.38, 0.94)	0.52 (0.32, 0.83)	0.64 (0.41, 0.99)	1.00 (0.53, 1.83)		
Natalizumab IV300	0.50 (0.42, 0.59)	0.81 (0.58, 1.15)	0.94 (0.73, 1.22)	0.78 (0.64, 0.96)	0.62 (0.47, 0.79)	0.65 (0.50, 0.82)	0.56 (0.42, 0.74)	0.69 (0.54, 0.87)	1.07 (0.66, 1.75)	1.07 (0.73, 1.57)	
Ocrelizumab IV600	0.44 (0.36, 0.55)	0.73 (0.55, 0.96)	0.84 (0.63, 1.14)	0.70 (0.56, 0.86)	0.55 (0.44, 0.70)	0.58 (0.47, 0.71)	0.50 (0.37, 0.69)	0.61 (0.53, 0.71)	0.96 (0.60, 1.53)	0.96 (0.61, 1.55)	0.89 (0.68, 1.19)

Table 84 Probability that each intervention will rank in each position for MRI T2 weighted lesions (fixed effects analysis; RRMS population)

	p_rank[1]	p_rank[2]	p_rank[3]	p_rank[4]	p_rank[5]	p_rank[6]	p_rank[7]	p_rank[8]	p_rank[9]	p_rank[10]	p_rank[11]	p_rank[12]
Placebo	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.15	1.00
Alemtuzumab IV12	0.00	0.02	0.08	0.16	0.33	0.63	0.89	0.95	0.98	0.99	1.00	1.00
Cladribine O3.5	0.03	0.13	0.30	0.53	0.85	0.96	1.00	1.00	1.00	1.00	1.00	1.00
Fingolimod O0.5	0.00	0.00	0.00	0.01	0.11	0.51	0.94	0.99	1.00	1.00	1.00	1.00
Glatiramer acetate SC20	0.00	0.00	0.00	0.00	0.00	0.00	0.02	0.11	0.32	0.78	0.98	1.00
Interferon beta 1a IM30	0.00	0.00	0.00	0.00	0.00	0.00	0.04	0.21	0.63	0.92	1.00	1.00
Interferon beta 1a SC22	0.00	0.00	0.00	0.00	0.00	0.00	0.02	0.07	0.15	0.32	0.87	1.00
Interferon beta 1a SC44	0.00	0.00	0.00	0.00	0.00	0.02	0.14	0.70	0.94	0.99	1.00	1.00
Interferon beta 1b IM 250	0.32	0.50	0.62	0.74	0.86	0.93	0.97	0.99	0.99	1.00	1.00	1.00
Natalizumab biosimilar	0.31	0.49	0.65	0.78	0.88	0.95	0.98	0.99	0.99	1.00	1.00	1.00
Natalizumab IV300	0.04	0.20	0.49	0.81	0.96	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Ocrelizumab IV600	0.30	0.67	0.86	0.96	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00

Any AEs (RRMS population)

Table 85 Comparison of results from fixed and random effects NMA for any AEs (RRMS population)

	Fixed Effects	Random effects
Intervention	**HR (95% Credible interval)**	**HR (95% Credible interval)**
Alemtuzumab IV12	0.91 (0.55, 1.47)	0.91 (0.54, 1.51)
Cladribine O3.5	1.10 (0.94, 1.29)	1.10 (0.92, 1.31)
Fingolimod O0.5	1.02 (0.94, 1.11)	1.02 (0.93, 1.13)
Glatiramer acetate SC20	1.01 (0.90, 1.12)	1.01 (0.89, 1.14)
Glatiramer acetate SC40	1.06 (0.85, 1.30)	1.06 (0.83, 1.35)
Interferon beta 1a IM30	1.07 (0.93, 1.24)	1.07 (0.91, 1.25)
Interferon beta 1a SC44	0.88 (0.55, 1.40)	0.88 (0.54, 1.44)
Interferon beta 1b IM 250	0.77 (0.51, 1.19)	0.76 (0.49, 1.19)
Natalizumab biosimilar	0.92 (0.65, 1.28)	0.91 (0.64, 1.30)
Natalizumab IV300	0.97 (0.85, 1.11)	0.97 (0.83, 1.12)
Ocrelizumab IV600	0.88 (0.56, 1.38)	0.88 (0.55, 1.41)
Ofatumumab SC20	1.02 (0.73, 1.42)	1.03 (0.71, 1.49)
Peginterferon beta 1a SC125	1.12 (0.98, 1.27)	1.12 (0.97, 1.28)
Ponesimod O20	1.04 (0.77, 1.39)	1.04 (0.77, 1.42)
Teriflunomide O14	1.03 (0.74, 1.41)	1.03 (0.74, 1.47)
Tau (95% CrI)	NA	0.03 (0.002, 0.11)
Mean log odds ratio	-0.02	-0.02
Residual deviance:	17.8 (on 25 data points)	18.7 (on 25 data points)
pD	14.8	16.1
DIC	32.6	34.8

Note: the random effects model had good convergence (all Rhat <1.01) so informative priors were not needed.

Chosen model: Fixed effects model

Figure 38 Model fit for any AEs assessed by individual study residual deviance (fixed effects analysis; RRMS population)

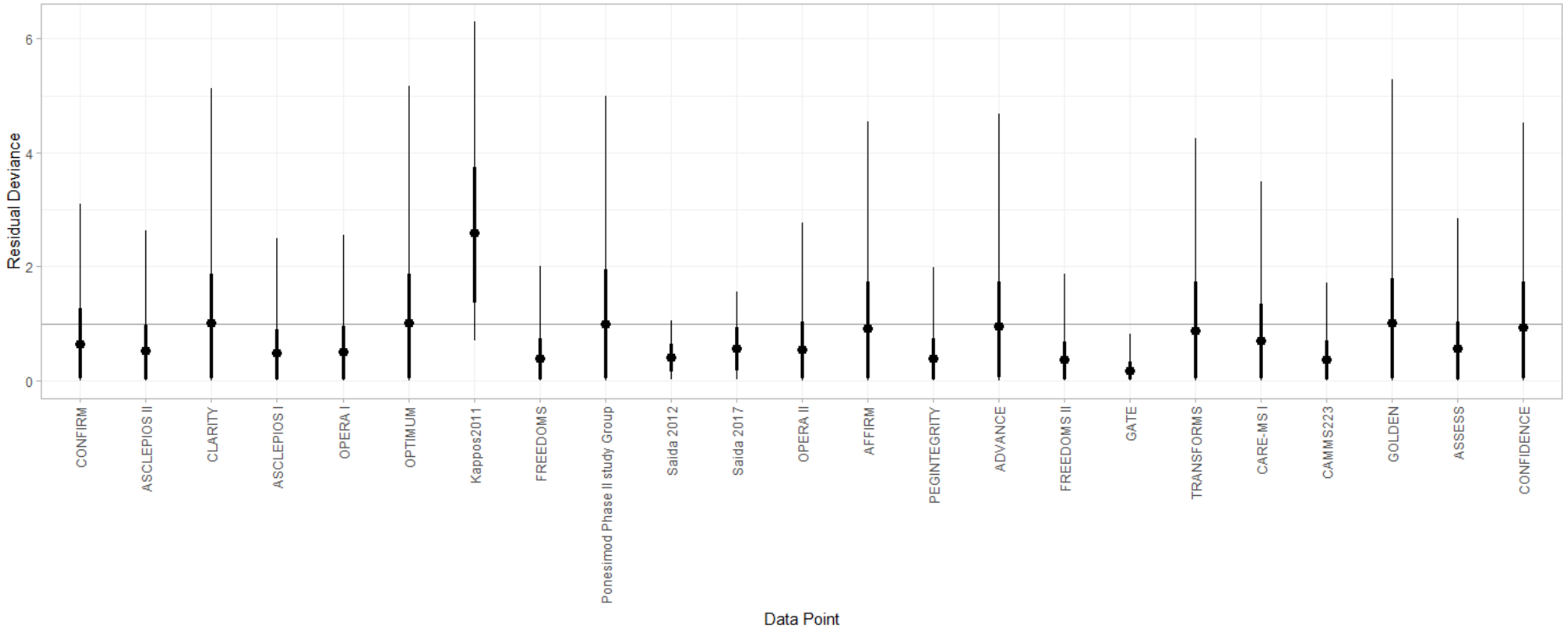

Table 86 Comparison (HR and 95% CrI) for each intervention pair for any AEs (fixed effects analysis; RRMS population)

	Placebo	Alemtuzumab IV12	Cladribine O3.5	Fingolimod O0.5	Glatiramer acetate SC20	Glatiramer acetate SC40	Interferon beta 1a IM30	Interferon beta 1a SC44	Interferon beta 1b IM 250	Natalizumab biosimilar	Natalizumab IV300	Ocrelizumab IV600	Ofatumumab SC20	Peginterferon beta 1a SC125	Ponesimod O20
Alemtuzumab IV12	0.91 (0.55, 1.47)														
Cladribine O3.5	1.10 (0.94, 1.29)	1.21 (0.73, 2.05)													
Fingolimod O0.5	1.02 (0.94, 1.11)	1.13 (0.69, 1.88)	0.93 (0.78, 1.11)												
Glatiramer acetate SC20	1.01 (0.90, 1.12)	1.11 (0.67, 1.86)	0.92 (0.76, 1.11)	0.99 (0.88, 1.11)											
Glatiramer acetate SC40	1.06 (0.85, 1.30)	1.16 (0.68, 2.00)	0.96 (0.74, 1.25)	1.03 (0.83, 1.27)	1.05 (0.87, 1.26)										
Interferon beta 1a IM30	1.07 (0.93, 1.24)	1.18 (0.71, 2.00)	0.98 (0.79, 1.20)	1.05 (0.92, 1.19)	1.06 (0.90, 1.25)	1.02 (0.79, 1.31)									
Interferon beta 1a SC44	0.88 (0.55, 1.40)	0.97 (0.83, 1.13)	0.80 (0.49, 1.30)	0.86 (0.54, 1.38)	0.87 (0.54, 1.41)	0.84 (0.50, 1.39)	0.82 (0.50, 1.33)								
Interferon beta 1b IM 250	0.77 (0.51, 1.19)	0.84 (0.43, 1.64)	0.70 (0.44, 1.10)	0.75 (0.50, 1.14)	0.76 (0.50, 1.17)	0.73 (0.45, 1.17)	0.71 (0.47, 1.11)	0.87 (0.46, 1.64)							
Natalizumab biosimilar	0.92 (0.65, 1.28)	1.01 (0.55, 1.85)	0.83 (0.57, 1.20)	0.90 (0.63, 1.27)	0.91 (0.63, 1.28)	0.87 (0.58, 1.29)	0.85 (0.59, 1.24)	1.04 (0.58, 1.86)	1.20 (0.68, 2.11)						
Natalizumab IV300	0.97 (0.85, 1.11)	1.07 (0.64, 1.80)	0.89 (0.73, 1.09)	0.95 (0.81, 1.11)	0.97 (0.81, 1.14)	0.92 (0.72, 1.18)	0.91 (0.75, 1.10)	1.10 (0.67, 1.80)	1.27 (0.80, 1.97)	1.06 (0.79, 1.45)					
Ocrelizumab IV600	0.88 (0.56, 1.38)	0.97 (0.81, 1.16)	0.80 (0.49, 1.29)	0.86 (0.54, 1.36)	0.87 (0.54, 1.39)	0.83 (0.50, 1.38)	0.82 (0.51, 1.31)	1.00 (0.90, 1.11)	1.15 (0.63, 2.14)	0.96 (0.54, 1.71)	0.90 (0.56, 1.45)				
Ofatumumab SC20	1.02 (0.73, 1.42)	1.13 (0.62, 2.02)	0.93 (0.65, 1.35)	1.00 (0.71, 1.40)	1.01 (0.71, 1.43)	0.97 (0.65, 1.45)	0.95 (0.66, 1.36)	1.16 (0.65, 2.05)	1.33 (0.77, 2.29)	1.12 (0.70, 1.77)	1.05 (0.74, 1.49)	1.16 (0.67, 2.05)			
Peginterferon beta 1a SC125	1.12 (0.98, 1.27)	1.23 (0.75, 2.08)	1.02 (0.84, 1.24)	1.09 (0.94, 1.27)	1.11 (0.93, 1.31)	1.06 (0.83, 1.36)	1.04 (0.88, 1.24)	1.27 (0.79, 2.09)	1.46 (0.93, 2.25)	1.22 (0.84, 1.77)	1.15 (0.96, 1.39)	1.27 (0.80, 2.05)	1.09 (0.77, 1.56)		
Ponesimod O20	1.04 (0.77, 1.39)	1.14 (0.65, 2.01)	0.94 (0.68, 1.31)	1.01 (0.74, 1.37)	1.03 (0.75, 1.40)	0.98 (0.68, 1.42)	0.97 (0.69, 1.33)	1.18 (0.68, 2.04)	1.35 (0.80, 2.28)	1.13 (0.73, 1.76)	1.07 (0.78, 1.47)	1.18 (0.68, 2.03)	1.01 (0.87, 1.19)	0.93 (0.67, 1.28)	
Teriflunomide O14	1.03 (0.74, 1.41)	1.13 (0.63, 2.01)	0.94 (0.66, 1.32)	1.01 (0.71, 1.41)	1.02 (0.73, 1.42)	0.97 (0.66, 1.42)	0.96 (0.68, 1.36)	1.17 (0.66, 2.04)	1.34 (0.79, 2.29)	1.12 (0.71, 1.77)	1.06 (0.75, 1.48)	1.17 (0.67, 2.04)	1.01 (0.92, 1.11)	0.92 (0.66, 1.30)	0.99 (0.88, 1.12)

Table 87 Probability that each intervention will rank in each position for any AEs (fixed effects analysis; RRMS population)

	p_rank[1]	p_rank[2]	p_rank[3]	p_rank[4]	p_rank[5]	p_rank[6]	p_rank[7]	p_rank[8]	p_rank[9]	p_rank[10]	p_rank[11]	p_rank[12]	p_rank[13]	p_rank[14]	p_rank[15]	p_rank[16]
Placebo	0.00	0.01	0.03	0.07	0.14	0.25	0.42	0.57	0.73	0.85	0.92	0.97	0.99	1.00	1.00	1.00
Alemtuzumab IV12	0.09	0.21	0.36	0.47	0.54	0.59	0.63	0.66	0.68	0.71	0.74	0.78	0.82	0.86	0.91	1.00
Cladribine O3.5	0.00	0.01	0.02	0.03	0.06	0.08	0.12	0.17	0.23	0.30	0.38	0.49	0.60	0.71	0.84	1.00
Fingolimod O0.5	0.00	0.01	0.02	0.05	0.10	0.17	0.27	0.39	0.52	0.65	0.78	0.87	0.94	0.98	1.00	1.00
Glatiramer acetate SC20	0.00	0.02	0.06	0.11	0.18	0.28	0.38	0.50	0.61	0.72	0.81	0.89	0.94	0.98	1.00	1.00
Glatiramer acetate SC40	0.01	0.04	0.07	0.11	0.17	0.23	0.29	0.34	0.41	0.47	0.54	0.61	0.70	0.79	0.88	1.00
Interferon beta 1a IM30	0.00	0.01	0.03	0.05	0.08	0.13	0.17	0.23	0.31	0.40	0.52	0.62	0.73	0.82	0.92	1.00
Interferon beta 1a SC44	0.09	0.29	0.47	0.56	0.61	0.66	0.69	0.72	0.75	0.78	0.81	0.84	0.87	0.92	0.97	1.00
Interferon beta 1b IM 250	0.49	0.58	0.63	0.76	0.82	0.85	0.87	0.89	0.91	0.92	0.94	0.95	0.96	0.97	0.98	1.00
Natalizumab biosimilar	0.14	0.30	0.36	0.44	0.57	0.62	0.66	0.72	0.75	0.78	0.82	0.85	0.88	0.91	0.94	1.00
Natalizumab IV300	0.01	0.06	0.15	0.23	0.35	0.50	0.59	0.68	0.77	0.83	0.88	0.92	0.96	0.98	1.00	1.00
Ocrelizumab IV600	0.10	0.26	0.44	0.56	0.63	0.67	0.70	0.73	0.75	0.79	0.82	0.85	0.88	0.94	0.98	1.00
Ofatumumab SC20	0.03	0.10	0.15	0.22	0.29	0.35	0.42	0.46	0.51	0.55	0.60	0.67	0.74	0.82	0.91	1.00
Peginterferon beta 1a SC125	0.00	0.00	0.01	0.01	0.02	0.04	0.06	0.09	0.14	0.20	0.29	0.40	0.54	0.67	0.83	1.00
Ponesimod O20	0.01	0.04	0.08	0.15	0.21	0.27	0.33	0.40	0.45	0.50	0.57	0.64	0.73	0.85	0.92	1.00
Teriflunomide O14	0.02	0.07	0.12	0.18	0.24	0.32	0.38	0.44	0.49	0.54	0.60	0.66	0.72	0.81	0.93	1.00

Serious Adverse Events (RRMS population)

Table 88 Comparison of results from fixed and random effects NMA for SAEs (RRMS population)

	Fixed Effects	Random effects
Intervention	**HR (95% Credible interval)**	**HR (95% Credible interval)**
Alemtuzumab IV12	1.05 (0.59, 1.84)	1.05 (0.56, 2.00)
Fingolimod O0.5	1.29 (0.79, 2.07)	1.31 (0.74, 2.31)
Cladribine O3.5	1.00 (0.78, 1.27)	1.02 (0.77, 1.38)
Glatiramer acetate SC20	0.82 (0.64, 1.07)	0.84 (0.62, 1.19)
Glatiramer acetate SC40	1.33 (0.53, 3.29)	1.37 (0.52, 3.56)
Interferon beta 1a IM30	0.91 (0.63, 1.30)	0.92 (0.61, 1.44)
Interferon beta 1a SC44	0.91 (0.58, 1.41)	0.92 (0.56, 1.54)
Interferon beta 1b IM 250	0.70 (0.46, 1.07)	0.71 (0.42, 1.21)
Natalizumab IV300	0.77 (0.58, 1.01)	0.75 (0.51, 1.06)
Ocrelizumab IV600	0.72 (0.40, 1.24)	0.72 (0.40, 1.38)
Ofatumumab SC20	1.60 (0.50, 5.05)	1.60 (0.46, 5.40)
Peginterferon beta 1a SC125	0.71 (0.50, 1.01)	0.72 (0.46, 1.11)
Ponesimod O20	1.49 (0.50, 4.21)	1.48 (0.48, 4.41)
Teriflunomide O14	1.39 (0.46, 4.11)	1.39 (0.42, 4.59)
Tau (95% CrI)	NA	0.11 (0.01, 0.33)
Mean log odds ratio	24.7 (on 32 data points)	24.2 (on 32 data points)
Residual deviance:	14.1	15.9
pD	38.8	40.1
DIC	1.05 (0.59, 1.84)	1.05 (0.56, 2.00)

Note: the random effects model had good convergence (all Rhat <1.01) so informative priors were not needed.

Chosen model: Fixed effects model

Figure 39 Model fit for SAEs assessed by individual study residual deviance (fixed effects analysis; RRMS population)

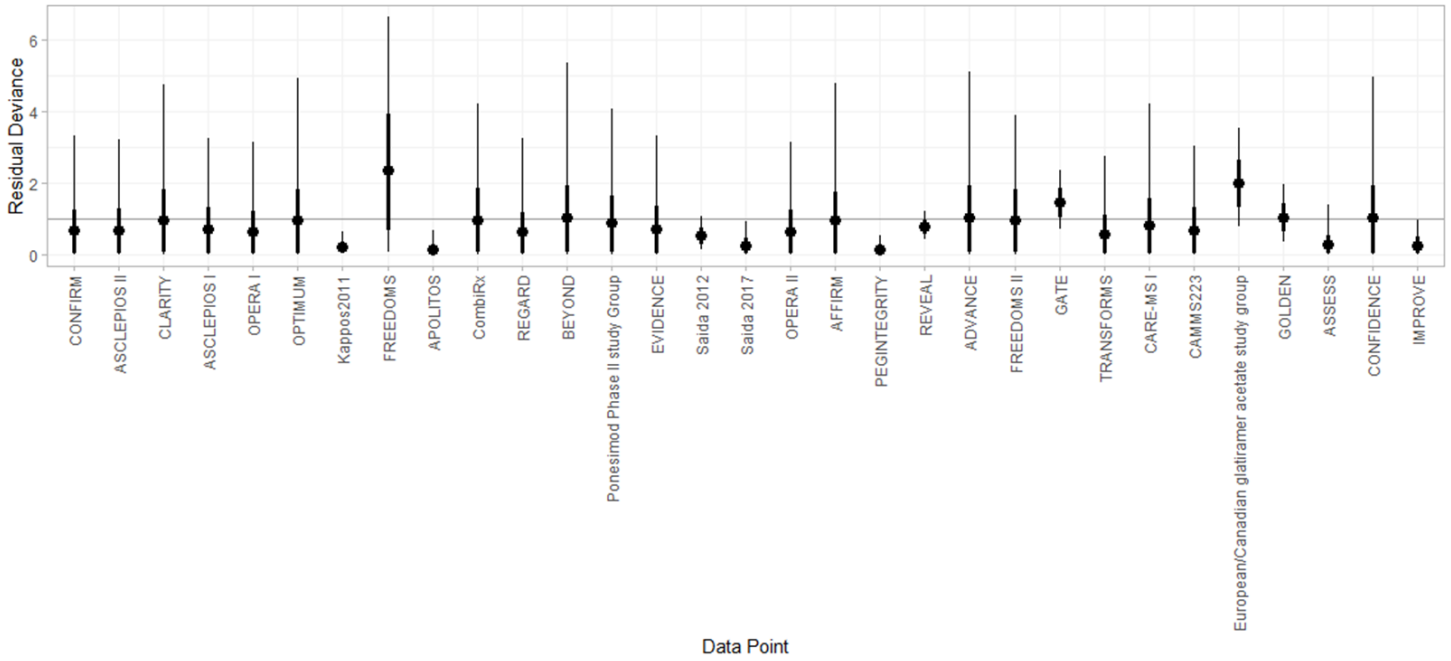

Table 89 Comparison (HR and 95% CrI) for each intervention pair for SAEs (fixed effects analysis; RRMS population)

	Placebo	Alemtuzumab IV12	Cladribine O3.5	Fingolimod O0.5	Glatiramer acetate SC20	Glatiramer acetate SC40	Interferon beta 1a IM30	Interferon beta 1a SC44	Interferon beta 1b IM 250	Natalizumab IV300	Ocrelizumab IV600	Ofatumumab SC20	Peginterferon beta 1a SC125	Ponesimod O20
Alemtuzumab IV12	1.05 (0.59, 1.84)													
Cladribine O3.5	1.29 (0.79, 2.07)	1.23 (0.59, 2.69)												
Fingolimod O0.5	1.00 (0.78, 1.27)	0.96 (0.53, 1.72)	0.77 (0.45, 1.33)											
Glatiramer acetate SC20	0.82 (0.64, 1.07)	0.78 (0.45, 1.37)	0.64 (0.37, 1.11)	0.82 (0.61, 1.11)										
Glatiramer acetate SC40	1.33 (0.53, 3.29)	1.27 (0.45, 3.52)	1.03 (0.37, 2.90)	1.33 (0.53, 3.37)	1.62 (0.67, 3.89)									
Interferon beta 1a IM30	0.91 (0.63, 1.30)	0.87 (0.49, 1.54)	0.70 (0.39, 1.30)	0.91 (0.63, 1.29)	1.11 (0.80, 1.54)	0.68 (0.27, 1.74)								
Interferon beta 1a SC44	0.91 (0.58, 1.41)	0.87 (0.61, 1.25)	0.70 (0.36, 1.34)	0.91 (0.57, 1.41)	1.10 (0.72, 1.65)	0.68 (0.26, 1.75)	1.00 (0.65, 1.53)							
Interferon beta 1b IM 250	0.70 (0.46, 1.07)	0.67 (0.36, 1.30)	0.54 (0.29, 1.01)	0.70 (0.45, 1.08)	0.85 (0.61, 1.18)	0.53 (0.20, 1.35)	0.77 (0.49, 1.23)	0.77 (0.46, 1.33)						
Natalizumab IV300	0.77 (0.58, 1.01)	0.73 (0.39, 1.39)	0.59 (0.34, 1.05)	0.76 (0.53, 1.10)	0.93 (0.64, 1.34)	0.58 (0.22, 1.53)	0.84 (0.54, 1.32)	0.85 (0.50, 1.44)	1.09 (0.65, 1.78)					
Ocrelizumab IV600	0.72 (0.40, 1.24)	0.68 (0.40, 1.15)	0.55 (0.27, 1.17)	0.71 (0.40, 1.25)	0.87 (0.50, 1.49)	0.54 (0.19, 1.48)	0.79 (0.45, 1.37)	0.79 (0.55, 1.11)	1.02 (0.54, 1.90)	0.93 (0.50, 1.73)				
Ofatumumab SC20	1.60 (0.50, 5.05)	1.53 (0.41, 5.60)	1.24 (0.35, 4.49)	1.60 (0.48, 5.02)	1.95 (0.59, 6.13)	1.21 (0.27, 5.38)	1.76 (0.51, 5.81)	1.77 (0.48, 5.91)	2.28 (0.67, 7.72)	2.09 (0.65, 6.77)	2.24 (0.60, 7.89)			
Peginterferon beta 1a SC125	0.71 (0.50, 1.01)	0.68 (0.35, 1.34)	0.55 (0.30, 1.02)	0.71 (0.46, 1.08)	0.86 (0.56, 1.34)	0.53 (0.20, 1.40)	0.78 (0.48, 1.31)	0.78 (0.45, 1.39)	1.01 (0.59, 1.76)	0.93 (0.60, 1.44)	0.99 (0.52, 1.89)	0.44 (0.13, 1.55)		
Ponesimod O20	1.49 (0.50, 4.21)	1.42 (0.41, 4.67)	1.15 (0.35, 3.73)	1.48 (0.50, 4.24)	1.81 (0.59, 5.20)	1.12 (0.27, 4.57)	1.63 (0.53, 4.97)	1.64 (0.50, 5.11)	2.12 (0.66, 6.68)	1.94 (0.65, 5.58)	2.08 (0.61, 6.87)	0.93 (0.56, 1.53)	2.09 (0.65, 6.26)	
Teriflunomide O14	1.39 (0.46, 4.11)	1.33 (0.36, 4.64)	1.08 (0.32, 3.71)	1.39 (0.44, 4.26)	1.69 (0.53, 5.17)	1.05 (0.25, 4.60)	1.53 (0.46, 4.83)	1.54 (0.44, 4.81)	1.98 (0.60, 6.30)	1.82 (0.60, 5.65)	1.95 (0.56, 6.61)	0.87 (0.63, 1.17)	1.96 (0.59, 6.25)	0.94 (0.63, 1.40)

Table 90 Probability that each intervention will rank in each position for SAEs (fixed effects analysis; RRMS population)

	p_rank[1]	p_rank[2]	p_rank[3]	p_rank[4]	p_rank[5]	p_rank[6]	p_rank[7]	p_rank[8]	p_rank[9]	p_rank[10]	p_rank[11]	p_rank[12]	p_rank[13]	p_rank[14]	p_rank[15]
Placebo	0.00	0.00	0.00	0.01	0.04	0.11	0.21	0.36	0.57	0.76	0.88	0.95	0.99	1.00	1.00
Alemtuzumab IV12	0.01	0.04	0.08	0.12	0.17	0.22	0.28	0.36	0.44	0.56	0.70	0.80	0.87	0.95	1.00
Cladribine O3.5	0.00	0.01	0.02	0.03	0.05	0.07	0.10	0.13	0.18	0.25	0.42	0.61	0.70	0.85	1.00
Fingolimod O0.5	0.00	0.00	0.01	0.03	0.07	0.14	0.24	0.38	0.55	0.72	0.85	0.92	0.97	0.99	1.00
Glatiramer acetate SC20	0.00	0.04	0.16	0.34	0.54	0.70	0.82	0.90	0.95	0.98	0.99	1.00	1.00	1.00	1.00
Glatiramer acetate SC40	0.04	0.07	0.10	0.13	0.15	0.18	0.21	0.24	0.28	0.33	0.42	0.58	0.64	0.74	1.00
Interferon beta 1a IM30	0.01	0.04	0.09	0.16	0.26	0.38	0.51	0.64	0.76	0.85	0.92	0.96	0.99	1.00	1.00
Interferon beta 1a SC44	0.00	0.05	0.12	0.20	0.30	0.40	0.52	0.63	0.74	0.84	0.90	0.95	0.98	1.00	1.00
Interferon beta 1b IM 250	0.24	0.45	0.61	0.73	0.81	0.87	0.91	0.95	0.97	0.98	0.99	0.99	1.00	1.00	1.00
Natalizumab IV300	0.09	0.25	0.41	0.55	0.67	0.78	0.86	0.92	0.95	0.98	0.99	1.00	1.00	1.00	1.00
Ocrelizumab IV600	0.27	0.44	0.56	0.66	0.74	0.80	0.86	0.91	0.94	0.96	0.97	0.99	1.00	1.00	1.00
Ofatumumab SC20	0.02	0.04	0.07	0.10	0.12	0.14	0.16	0.18	0.20	0.23	0.27	0.33	0.47	0.67	1.00
Peginterferon beta 1a SC125	0.24	0.43	0.58	0.68	0.77	0.84	0.90	0.94	0.96	0.98	0.99	1.00	1.00	1.00	1.00
Ponesimod O20	0.02	0.04	0.08	0.10	0.13	0.15	0.18	0.20	0.23	0.26	0.31	0.42	0.65	0.83	1.00
Teriflunomide O14	0.05	0.10	0.13	0.16	0.18	0.21	0.23	0.26	0.28	0.33	0.39	0.51	0.76	0.97	1.00

Discontinuation due to AEs (RRMS population)

Table 91 Comparison of results from fixed and random effects NMA for discontinuation due to AEs (RRMS population)

	Fixed Effects	Random effects
Intervention	**HR (95% Credible interval)**	**HR (95% Credible interval)**
Alemtuzumab IV12	0.42 (0.14, 1.14)	0.45 (0.13, 1.54)
Cladribine O3.5	1.68 (0.75, 3.78)	1.68 (0.56, 5.11)
Fingolimod O0.5	1.54 (1.16, 2.02)	1.63 (1.08, 2.64)
Glatiramer acetate SC20	2.15 (1.43, 3.27)	2.21 (1.25, 3.99)
Glatiramer acetate SC40	1.84 (1.00, 3.32)	1.86 (0.83, 4.16)
Interferon beta 1a IM30	1.53 (0.89, 2.59)	1.70 (0.87, 3.77)
Interferon beta 1a SC44	2.10 (1.19, 3.73)	2.29 (1.04, 5.29)
Interferon beta 1b IM 250	2.22 (1.04, 4.71)	2.41 (1.02, 6.19)
Natalizumab biosimilar	2.87 (0.67, 12.07)	2.63 (0.47, 14.21)
Natalizumab IV300	1.37 (0.75, 2.47)	1.27 (0.53, 2.85)
Ocrelizumab IV600	1.24 (0.59, 2.54)	1.37 (0.52, 3.88)
Peginterferon beta 1a SC125	3.48 (1.46, 8.36)	3.50 (1.24, 9.82)
Tau (95% CrI)	NA	0.27 (0.01, 0.69)
Mean log odds ratio	0.52	0.55
Residual deviance:	29.2 (on 28 data points)	26 (on 28 data points)
pD	12	15.7
DIC	41.2	41.7

Note: the random effects model had good convergence (all Rhat <1.01) so informative priors were not needed.

Chosen model: Fixed effects model

Figure 40 Model fit for discontinuation due to AEs assessed by individual study residual deviance (fixed effects analysis; RRMS population)

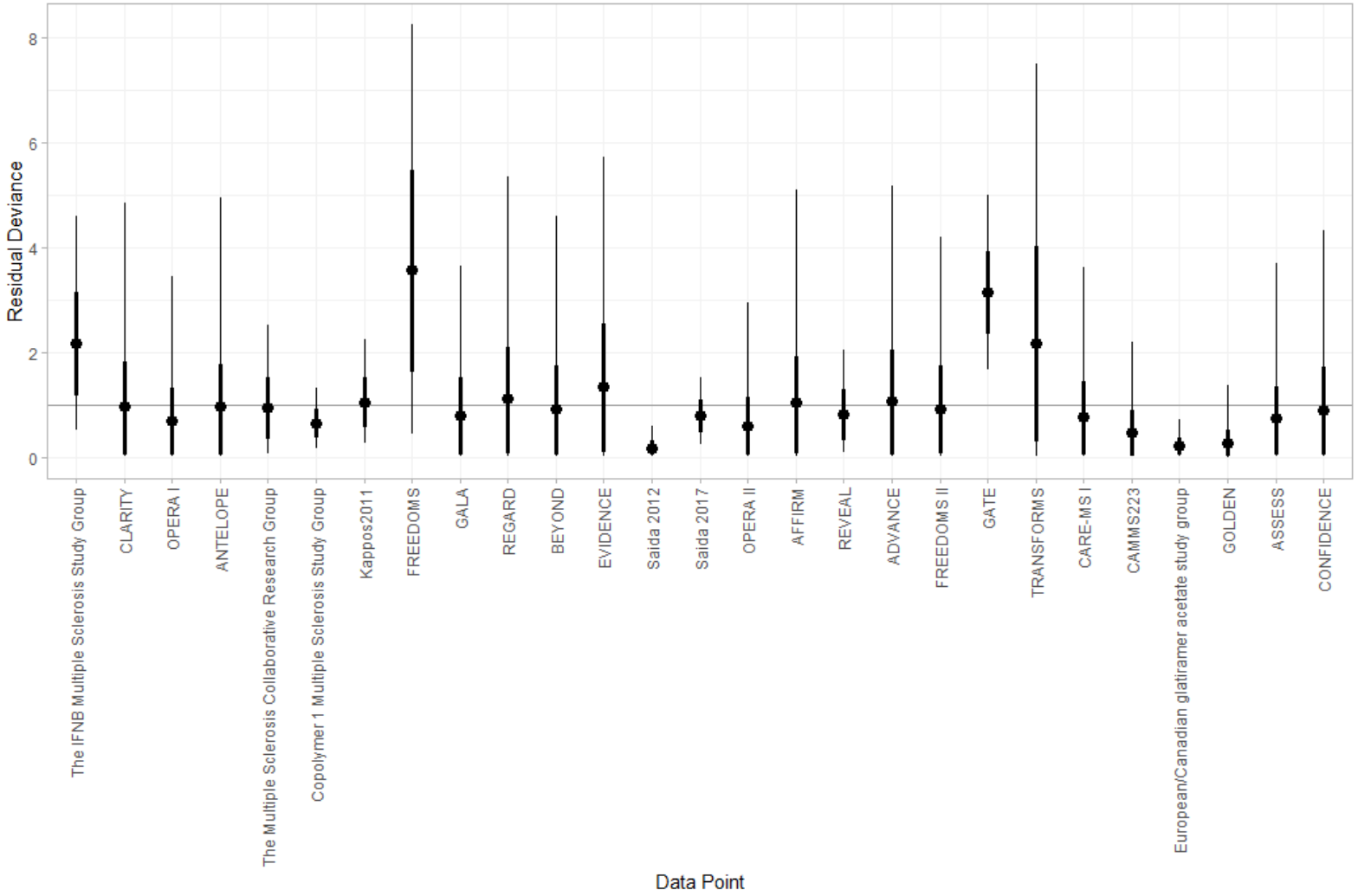

Table 92 Comparison (RR and 95% CrI) for each intervention pair for discontinuation due to AEs (fixed effects analysis; RRMS population)

	Placebo	Alemtuzumab IV12	Cladribine O3.5	Fingolimod O0.5	Glatiramer acetate SC20	Glatiramer acetate SC40	Interferon beta 1a IM30	Interferon beta 1a SC44	Interferon beta 1b IM 250	Natalizumab biosimilar	Natalizumab IV300	Ocrelizumab IV600
Alemtuzumab IV12	0.42 (0.14, 1.14)											
Cladribine O3.5	1.68 (0.75, 3.78)	4.04 (1.14, 14.59)										
Fingolimod O0.5	1.54 (1.16, 2.02)	3.71 (1.37, 10.17)	0.92 (0.39, 2.16)									
Glatiramer acetate SC20	2.15 (1.43, 3.27)	5.18 (1.86, 14.34)	1.28 (0.53, 3.21)	1.40 (0.97, 2.00)								
Glatiramer acetate SC40	1.84 (1.00, 3.32)	4.42 (1.39, 13.89)	1.09 (0.40, 2.96)	1.19 (0.65, 2.21)	0.85 (0.47, 1.52)							
Interferon beta 1a IM30	1.53 (0.89, 2.59)	3.67 (1.28, 10.45)	0.91 (0.36, 2.36)	0.99 (0.58, 1.61)	0.71 (0.41, 1.22)	0.83 (0.40, 1.74)						
Interferon beta 1a SC44	2.10 (1.19, 3.73)	5.06 (2.16, 12.11)	1.25 (0.49, 3.42)	1.36 (0.79, 2.36)	0.98 (0.58, 1.64)	1.15 (0.55, 2.39)	1.38 (0.81, 2.31)					
Interferon beta 1b IM 250	2.22 (1.04, 4.71)	5.35 (1.55, 18.48)	1.33 (0.46, 3.99)	1.44 (0.69, 3.00)	1.03 (0.52, 2.10)	1.21 (0.49, 2.97)	1.46 (0.63, 3.32)	1.06 (0.45, 2.43)				
Natalizumab biosimilar	2.87 (0.67, 12.07)	6.91 (1.14, 42.03)	1.71 (0.33, 8.88)	1.86 (0.44, 8.19)	1.33 (0.31, 5.82)	1.56 (0.35, 7.52)	1.88 (0.44, 9.02)	1.36 (0.30, 6.44)	1.29 (0.26, 6.37)			
Natalizumab IV300	1.37 (0.75, 2.47)	3.30 (1.00, 11.22)	0.82 (0.30, 2.24)	0.89 (0.46, 1.74)	0.64 (0.32, 1.30)	0.75 (0.32, 1.74)	0.90 (0.40, 2.04)	0.65 (0.29, 1.48)	0.62 (0.24, 1.62)	0.48 (0.13, 1.76)		
Ocrelizumab IV600	1.24 (0.59, 2.54)	2.97 (1.15, 7.98)	0.74 (0.25, 2.19)	0.80 (0.40, 1.63)	0.57 (0.29, 1.12)	0.67 (0.29, 1.58)	0.81 (0.42, 1.62)	0.59 (0.38, 0.94)	0.56 (0.22, 1.43)	0.43 (0.09, 2.06)	0.90 (0.35, 2.29)	
Peginterferon beta 1a SC125	3.48 (1.46, 8.36)	8.38 (2.24, 31.99)	2.08 (0.63, 6.89)	2.26 (0.90, 5.66)	1.62 (0.62, 4.43)	1.90 (0.66, 5.66)	2.28 (0.83, 6.29)	1.66 (0.58, 4.76)	1.57 (0.50, 5.00)	1.21 (0.22, 6.28)	2.54 (0.90, 7.53)	2.82 (0.92, 8.82)

Table 93 Probability that each intervention will rank in each position for discontinuation due to AEs (fixed effects analysis; RRMS population)

	p_rank[1]	p_rank[2]	p_rank[3]	p_rank[4]	p_rank[5]	p_rank[6]	p_rank[7]	p_rank[8]	p_rank[9]	p_rank[10]	p_rank[11]	p_rank[12]	p_rank[13]
Placebo	0.03	0.49	0.84	0.96	0.99	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Alemtuzumab IV12	0.92	0.97	0.98	0.99	0.99	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Cladribine O3.5	0.01	0.09	0.17	0.27	0.36	0.45	0.53	0.62	0.70	0.79	0.88	0.97	1.00
Fingolimod O0.5	0.00	0.00	0.04	0.15	0.37	0.60	0.81	0.92	0.98	0.99	1.00	1.00	1.00
Glatiramer acetate SC20	0.00	0.00	0.00	0.00	0.01	0.03	0.10	0.22	0.44	0.69	0.89	0.98	1.00
Glatiramer acetate SC40	0.00	0.01	0.05	0.12	0.21	0.31	0.42	0.56	0.69	0.81	0.92	0.98	1.00
Interferon beta 1a IM30	0.00	0.03	0.11	0.26	0.42	0.58	0.73	0.84	0.92	0.97	0.99	1.00	1.00
Interferon beta 1a SC44	0.00	0.00	0.00	0.02	0.05	0.11	0.20	0.33	0.49	0.67	0.85	0.97	1.00
Interferon beta 1b IM 250	0.00	0.01	0.03	0.07	0.11	0.17	0.24	0.32	0.43	0.56	0.74	0.91	1.00
Natalizumab biosimilar	0.01	0.06	0.09	0.13	0.17	0.21	0.24	0.28	0.33	0.39	0.46	0.65	1.00
Natalizumab IV300	0.01	0.11	0.27	0.44	0.58	0.70	0.79	0.86	0.92	0.96	0.99	1.00	1.00
Ocrelizumab IV600	0.01	0.23	0.41	0.58	0.71	0.80	0.88	0.93	0.97	0.98	1.00	1.00	1.00
Peginterferon beta 1a SC125	0.00	0.00	0.01	0.01	0.03	0.04	0.07	0.10	0.13	0.18	0.28	0.55	1.00

ARR (HARR MS population)

Table 94 Comparison of results from fixed and random effects NMA for ARR (HARRMS population)

	Fixed Effects	Random effects
Intervention	**RR (95% Credible interval)**	**RR (95% Credible interval)**
Alemtuzumab IV12	0.53 (0.30, 0.92)	0.64 (0.00, 200.49)
Cladribine O3.5	0.57 (0.33, 0.97)	0.57 (0.02, 22.18)
Fingolimod O0.5	0.52 (0.39, 0.69)	0.56 (0.02, 18.53)
Interferon beta 1a	1.03 (0.64, 1.67)	1.23 (0.02, 143.02)
Natalizumab IV300	0.31 (0.15, 0.63)	0.32 (0.01, 11.88)
Ocrelizumab IV600	0.33 (0.15, 0.69)	0.38 (0.00, 102.99
Tau (95% CrI)	NA	1.40 (0.05,3.95)
Mean log odds ratio	-0.69	-0.58
Residual deviance:	8.1 (on 8 data points)	8 (on 8 data points)
pD	8.1	8
DIC	16.2	16.1

Note: all Rhat <1.01

RE parameters:

seed	437219664
trt_effects	"random"
prior_intercept	normal(0, scale = 10)
prior_trt	normal(0, scale = 5)
prior_het	half_normal(scale = 2)
control = list	max_treedepth = 12
adapt_delta	0.99

Chosen model: Fixed effects model

Figure 41 Model fit for ARR assessed by individual study residual deviance (fixed effects analysis; HARRMS population)

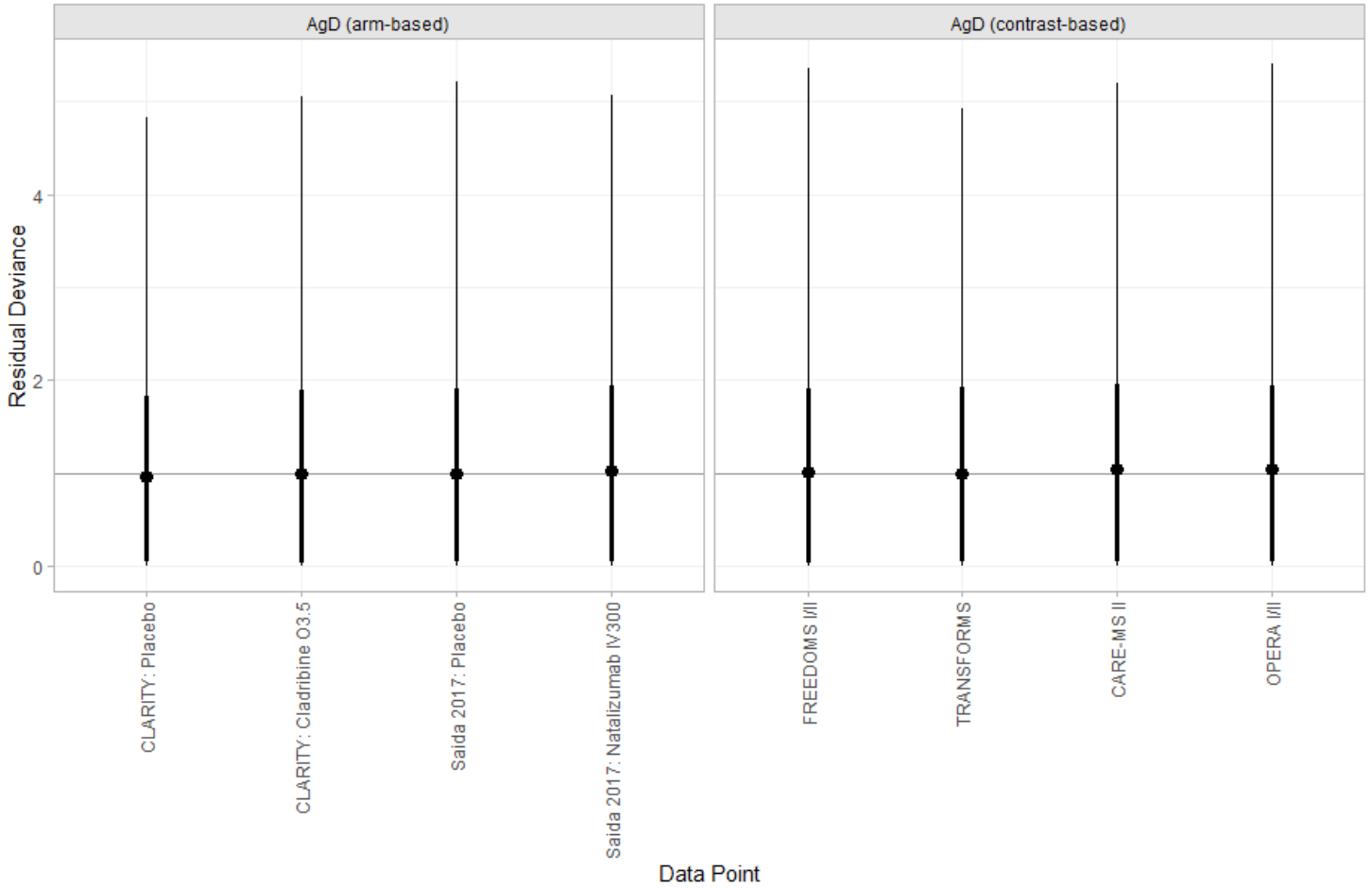

Table 95 Comparison (RR and 95% CrI) for each intervention pair for ARR (random effects analysis; HARRMS population)

	Placebo	Alemtuzumab IV12	Cladribine O3.5	Fingolimod O0.5	Interferon beta 1a	Natalizumab IV300
Alemtuzumab IV12	0.53 (0.30, 0.92)					
Cladribine O3.5	0.57 (0.33, 0.97)	1.08 (0.49, 2.39)				
Fingolimod O0.5	0.52 (0.39, 0.69)	0.99 (0.61, 1.60)	0.91 (0.50, 1.69)			
Interferon beta 1a	1.03 (0.64, 1.67)	1.97 (1.52, 2.56)	1.82 (0.87, 3.83)	1.99 (1.33, 2.97)		
Natalizumab IV300	0.31 (0.15, 0.63)	0.59 (0.24, 1.43)	0.54 (0.22, 1.39)	0.59 (0.28, 1.29)	0.30 (0.13, 0.70)	
Ocrelizumab IV600	0.33 (0.15, 0.69)	0.62 (0.33, 1.17)	0.58 (0.23, 1.43)	0.63 (0.31, 1.29)	0.32 (0.18, 0.56)	1.06 (0.38, 3.00)

Table 96 Probability that each intervention will rank in each position for ARR (random effects analysis; HARRMS population)

	p_rank[1]	p_rank[2]	p_rank[3]	p_rank[4]	p_rank[5]	p_rank[6]	p_rank[7]
Placebo	0.00	0.00	0.00	0.00	0.02	0.57	1.00
Alemtuzumab IV12	0.01	0.12	0.43	0.70	0.99	1.00	1.00
Cladribine O3.5	0.02	0.13	0.33	0.53	0.94	0.99	1.00
Fingolimod O0.5	0.00	0.09	0.39	0.83	1.00	1.00	1.00
Interferon beta 1a	0.00	0.00	0.00	0.00	0.05	0.45	1.00
Natalizumab IV300	0.53	0.83	0.92	0.96	1.00	1.00	1.00
Ocrelizumab IV600	0.44	0.84	0.93	0.97	1.00	1.00	1.00

Appendix 6
Details on economic models in previous relevant TAs

Table 97 Summary of economic evaluations of Highly Active Relapse Remitting Multiple Sclerosis technologies with marketing authorisation in the UK

TA (year) Intervention	Model type	Time horizon	Discount Rate	Population	Comparators	Outcomes and sources of data
TA767 (2022) Ponesimod (Ponvory, Janssen)[42]	Markov Cohort Model	Lifetime 50 years (annual cycles)	3.5 %	RRMS *Subgroup:* HA RRMS	RRMS • Beta interferons, • Dimethyl fumarate, • Glatiramer acetate, • Teriflunomide, • Ocrelizumab, • Peginterferon beta-1a • Ofatumumab. HA RRMS • Alemtuzumab • Fingolimod • Cladribine, • Ofatumumab and • Ocrelizumab (only if alemtuzumab is contraindicated or otherwise unsuitable)	Intervention: ARR, CDP-3, CDP-6, AEs from OPTIMUM, OPTIMUM-LT Comparators: ARR, DCP-3, CDP-6, All cause discontinuation from NMA (RRMS), NMA (HA RRMS) Natural History: RRMS transitions from the British Columbia Multiple Sclerosis registry,[128] HA RRMS transitions from the AFFIRM trial. Converting from RRMS to SPMS from the London, Ontario MS database.[129] ARR by EDSS[129] Relative risk of relapse from the AFFIRM trial. Relative risk of death applied to EDSS states.[166]

TA (year) Intervention	Model type	Time horizon	Discount Rate	Population	Comparators	Outcomes and sources of data
TA699 (2021) Ofatumumab (Kesimpta, Novartis)[41]	Markov Cohort Model	Lifetime 62 years (annual cycles)	3.5 %	RRMS *Subgroups:* HA RRMS & RES RRMS were not considered suitable for decision making	RRMS • Beta interferons, • Dimethyl fumarate, • Glatiramer acetate, • Teriflunomide, • Peginterferon beta-1a	Intervention: ARR, CDP-3, CDP-6, AEs , EQ-5D from ASCLEPIOS I, ASCLEPIOS II Comparators: ARR, DCP-3, CDP-6, All cause discontinuation from NMA (RRMS) Natural History: RRMS transitions from the British Columbia Multiple Sclerosis registry,[128]. Converting from RRMS to SPMS from the London, Ontario MS database[129] supplemented by the EXPAND trial. ARR by EDSS[129] Relative risk of relapse from the AFFIRM trial. Relative risk of death applied to EDSS states.[166]
TA616 (2019) Cladribine tablets (Mavenclad, Merck Serono)[38]	Markov Cohort Model	Lifetime 50 years (annual cycles)	3.5 %	RES RRMS SOT RRMS	RES RRMS • Alemtuzumab • Natalizumab • Daclizumab (contra indicated to alemtuzumab) SOT RRMS • Alemtuzumab • Fingolimod • Daclizumab (contra indicated to alemtuzumab)	Intervention & Comparators relative treatment effects: ARR, DCP-3, CDP-6, relapse free patients, AEs (grades 3 or 4), discontinuation due to AEs, all cause discontinuation from NMA & Meta-regressions per sub-group (RES RRMS, SOT RRMS) Intervention: EQ-5D from ASCLEPIOS I Natural History: RRMS transitions from the British Columbia Multiple Sclerosis registry,[128]. Faster rates of progression for the SOT RRMS & RES RRMS groups based on CLARITY. ARR independent of EDSS, year1 pbo arm of CLARITY, subsequent years as a function of time from the British Columbia Multiple Sclerosis registry.[177] Relative risk of death from a meta-analysis of SMRs.[343]

TA (year) Intervention	Model type	Time horizon	Discount Rate	Population	Comparators	Outcomes and sources of data
TA533 (2018) Ocrelizumab (Ocrevus, Roche)[33]	Multi-state Markov Cohort Model	Lifetime 50 years (annual cycles)	3.5 %	RRMS *Subgroups:* HA RRMS RES RRMS	RRMS • Alemtuzumab, • Beta interferons, • Dimethyl fumarate, • Glatiramer acetate, • Natalizumab, • Fingolimod. HA RRMS • Alemtuzumab • Fingolimod RES RRMS • Alemtuzumab • Natalizumab	Intervention: ARR, DCP-3, CDP-6, AEs, EQ-5D from OPERA I - OPERA II - OPERA OLE Comparators: ARR, DCP-3, CDP-6, All cause discontinuation, NMA (RRMS) - NMA (HA RRMS) - NMA (RES RRMS) Natural History: RRMS transitions from the British Columbia Multiple Sclerosis registry,[128] HA RRMS transitions from the AFFIRM trial. Converting from RRMS to SPMS from the London, Ontario MS database.[129] ARR by EDSS.[129] Relative risk of relapse from the AFFIRM trial. Relative risk of death applied to EDSS states[166]
TA312 (2014, update 2020) Alemtuzumab (Lemtrada, Sanofi)[39]	Multi-state Markov Cohort Model	Lifetime 50 years (annual cycles)	3.5 %	RRMS *Subgroups:* HA RRMS RES RRMS	RRMS • Beta interferons, • Glatiramer acetate, HA RRMS • Fingolimod RES RRMS • Natalizumab	Intervention & Comparators relative treatment effects: ARR, SAD-3, SAD-6, relapse free patients, discontinuation due to AEs from NMAs per group / sub-group (RRMS, HA RRMS and RES RRMS) Intervention: AEs, SAEs, EQ-5D from CAMMS223, CARE-MS I & II Natural History: RRMS transitions EDSS (1-9) and converting from RRMS to SPMS were sourced from the London Ontario MS database.[129] RRMSEDSS 0 from the placebo arms of TOWER & TEMSO trials ARR by EDSS[129] Relative risk of death applied to EDSS states[166]

TA (year) Intervention	Model type	Time horizon	Discount Rate	Population	Comparators	Outcomes and sources of data
TA254 (2012) Fingolimod (Gilenya, Novartis)[40]	Markov Cohort Model	Lifetime 50 years (annual cycles)	3.5 %	Main analysis: 1b)HA RRMS In DP not in CE analysis: 1a)HA RRMS 2)RES RRMS	1b)HA RRMS • beta interferon-1a (Avonex) • Rebif-22 • Rebif-44 • Betaferon • Extavia	Intervention ARR, SAD-3, SAD-6 from the TRANSFORMS & FREEDOMS trials. Comparators: ARR, SAD-3, SAD-6 from NMAs (HA RRMS) Natural History: RRMS transitions EDSS (1-9) and converting from RRMS to SPMS from the London, Ontario MS database .[117] ARR by EDSS[129] Relative risk of death applied to EDSS states.[166]
TA127 (2007) (Tysabri, Biogen Inc)[34]	Multi-state Markov Cohort Model	Lifetime 20 years (annual cycles)	3.5 %	RES RRMS SOT RRMS	• Beta interferons, • Glatiramer acetate.	Intervention ARR, SAD-3, SAD-6 from AFFIRM. Comparators: ARR, SAD-3, SAD-6 from pairwise meta-analyses Natural History: RRMS transitions EDSS (1-9) and converting from RRMS to SPMS from the London, Ontario MS database .[117] } HA RRMS transitions from the AFFIRM trial. ARR by EDSS[129] Relative risk of death applied to EDSS states[166]

Table 98 (continued) Summary of economic evaluations of Highly Active Relapse Remitting Multiple Sclerosis technologies with marketing authorisation in the UK

TA, year	Health states	Utilities & Costs	EAG key Criticism	Results
TA767 (2022) Ponesimod (Ponvory, Janssen)[42]	20 in total: • 10 EDSS RRMS • 9 EDSS SPMS • Death	• RRMS EQ-5D EDSS 0-9, • SPMS Utility decrement • Caregiver disutilities • Relapse HS disutilities • AE utility decrements • Drug acquisition, administration and monitoring costs • HS Costs EDSS 0-9, • AE Costs	**Treatment switching or sequencing** – The EAG acknowledged the availability of data a limitation on modelling this aspect of clinical practice, leading to an oversimplified model. **Implausible no. of patients in high EDSS states** – Contrary to the expert opinion of clinical advisors a higher proportion of patients than would be observed in practice progressed to EDSS 8 and 9 where they accumulated negative QALYs. The EAG was critical of this aspect of the model, despite it being broadly in line with other appraisals. The committee concluded that this model, as with other multiple sclerosis models, was limited in its ability to accurately reflect the course of the condition. **More appropriate data on mortality** - Clinical experts considered the mortality data was outdated and that managing acute infection and nursing has fundamentally reduced mortality with MS. That new standardised mortality rates by EDSS state had been recently published. The committee concluded that in future appraisals in MS, it would like to see more appropriate sources of mortality data in a model with plausible distributions of people in EDSS states.	The committee concluded that overall, the cost-effectiveness results were acceptable and the most likely estimates were below what NICE considers an acceptable use of NHS resources
TA699 (2021) Ofatumumab (Kesimpta, Novartis)[41]	21 in total: • 10 EDSS RRMS • 10 EDSS SPMS • Death	• RRMS EQ-5D EDSS 0-9, • SPMS Utility decrement • Caregiver disutilities	**loss of treatment effectiveness** – The committee refereed to TA533 (Ocrelizumab) which had accepted treatment discontinuation as proxy for loss of effectiveness over time, despite lack of evidence on waning from the key trials.	The committee referred to the appraisal guidelines stating that, above a most plausible ICER of £20,000 per quality-adjusted life year (QALY) gained, judgements about the acceptability of a technology as an effective use of NHS resources

TA, year	Health states	Utilities & Costs	EAG key Criticism	Results
		• Relapse HS disutilities • AE utility decrements • Drug acquisition, administration and monitoring costs • HS Costs EDSS 0-9, • AE Costs	**Implausible relapse rates in higher EDSS states** – Contrary to clinical advice the company modelled increasing relapse rates at the higher EDSS SPMS states. The EAG went with values that were decreasing as severity increased, reported in TA 527. **Conflicting approaches to converting from RRMS to SPMS** – the company used transition matrices from the British Columbia longitudinal multiple sclerosis dataset (TA254). The EAG preferred to use transition matrices from the London Ontario multiple sclerosis dataset (TA624) Both data sources had been accepted previously by NICE technology appraisal committees and were found to have minimal impact on the ICERs.	will take into account the degree of certainty around the ICER. The committee noted that, with the exception of waning of treatment effect, changes to each assumption had a minor impact on the base-case ICER. The committee concluded that it could recommend ofatumumab as an additional treatment option for relapsing–remitting multiple sclerosis.
TA616 (2019) Cladribine tablets (Mavenclad, Merck Serono)[38]	11 in total: • 10 EDSS RRMS • Death	• RRMS EQ-5D EDSS 0-9, • Caregiver disutilities • Relapse HS disutilities • AE utility decrements • Drug acquisition, administration and monitoring costs • HS Costs EDSS 0-9, • AE Costs	**Inaccurate RES RRMS & SOT RRMS natural history** - The company calculating different rates of disability progression in the subgroups. The clinical experts and the EAG explained that, although assuming different rates of disease progression for each subgroup was reasonable, the company's approach was simplistic and potentially inaccurate. The committee appreciated that there was no clear alternative data source or method, and was aware that such adjustment had not been used in previous technology appraisals. **loss of treatment effectiveness** – The company used treatment switching analysis to support their assumption; treatment waning for Cladribine to begin 2 years later than comparators. The committee noted that there was no statistically significant evidence to support different waning effects and that patient numbers used for the analysis in the subgroups were very small. It concluded that the company's evidence	Cladribine dominated all other treatments in both RES RRMS and SOT RRMS groups. Cladribine was more effective and cheaper than fingolimod and natalizumab. It was less effective and cheaper than alemtuzumab. The ICERs vs. alemtuzumab were: • £219,549 gained per QALY lost (RES RRMS) • £372,802 gained per QALY lost SOT (RRMS) The committee concluded that cladribine was a cost-effective use of NHS resources for rapidly evolving severe relapsing–remitting multiple sclerosis and sub optimally treated relapsing–remitting multiple sclerosis.

TA, year	Health states	Utilities & Costs	EAG key Criticism	Results
			was insufficient to justify using a different treatment waning assumption for cladribine. **Treatment stopping rates are not constant** - The EAG explained that people are more likely to stop treatment during the first year of treatment than in a subsequent year. Therefore, the company's approach of applying trial-based discontinuation rates to subsequent years would overestimate the number of people stopping treatment.	
TA533 (2018) Ocrelizumab (Ocrevus, Roche)[33]	31 in total: • 20 EDSS RRMS • 10 EDSS SPMS • Death	• RRMS EQ-5D EDSS 0-9, • SPMS Utility decrement • Caregiver disutilities • Relapse HS disutilities • AE utility decrements • Drug acquisition, administration and monitoring costs • HS Costs EDSS 0-9, • AE Costs	**loss of treatment effectiveness** – In clinical practice, when a drug is no longer effective, patients switch on to alternative treatments. Treatment switching was not included in the model. The EAG accepted treatment discontinuation as proxy for loss of effectiveness over time, despite lack of evidence on waning from the key trials.	The most plausible ICERs were below £30,000 per QALY gained in the relapsing–remitting multiple sclerosis population compared with all relevant comparators, apart from alemtuzumab, which dominated all comparisons. In the highly active subgroup, the most plausible ICER for ocrelizumab compared with fingolimod was below £20,000 per QALY gained. In the rapidly evolving severe subgroup, ocrelizumab was cheaper and less effective than natalizumab. The most plausible ICER for ocrelizumab compared with natalizumab was In the range of £350,000 to £125,000 saved per QALY lost .
TA312 (2014, update 2020) Alemtuzumab (Lemtrada, Sanofi)[39]	20 in total: • 10 EDSS RRMS • 9 EDSS SPMS • Death	• RRMS EQ-5D EDSS 0-9, • SPMS Utility decrement • Caregiver disutilities	**loss of treatment effectiveness** – The company assumed treatment with Alemtuzumab would persist indefinitely. The clinical specialists also stated that people who experience a relapse soon after treatment with alemtuzumab will probably be offered alternative treatment. The Committee stated that, for some	The most plausible ICER for alemtuzumab compared with glatiramer acetate for people with active relapsing-remitting multiple sclerosis is likely to lie between £13,600 and £24,500 per QALY gained active relapsing–remitting multiple sclerosis.

TA, year	Health states	Utilities & Costs	EAG key Criticism	Results
		• Relapse HS disutilities • AE utility decrements • Drug acquisition, administration and monitoring costs • HS Costs EDSS 0-9, • AE Costs	people, alemtuzumab might not provide long-term enduring effect and other treatments might be required. The Committee concluded that because of the uncertainty about the long-term treatment effects it was appropriate to incorporate waning effects into the model.	The most plausible ICER for patients with highly active relapsing-remitting multiple sclerosis despite beta interferon treatment was £8900 per QALY gained for alemtuzumab compared with fingolimod. Alemtuzumab dominated natalizumab (that is, less expensive and more effective) for patients with rapidly evolving severe relapsing-remitting multiple sclerosis.
TA254 (2012) Fingolimod (Gilenya, Novartis)[344]	21 in total: • 10 EDSS RRMS • 10 EDSS SPMS • Death	• RRMS EQ-5D EDSS 0-9, • SPMS Utility decrement • Caregiver disutilities • Relapse HS disutilities • AE utility decrements • Drug acquisition, administration and monitoring costs • HS Costs EDSS 0-9, • AE Costs	**Uncertainty in the analysis on the population of interest -** analysis of population 1b that excluded people who also met the criteria for population 2 (that is, a population in which people with rapidly evolving severe disease were excluded) was provided. The Committee noted that this analysis generated lower ICERs than those for the whole of population 1b, but was aware of reservations expressed by the manufacturer and the EAG about the small samples on which the subgroup analysis was based **Uncertainty around the improvements in quality of life -** There weren't statistically significant changes from baseline for EQ-5D measures observed for people with relapsing–remitting multiple sclerosis treated with fingolimod or placebo in the FREEDOMS trial. A slight, non-statistically significant improvement in the PRIMUS-QoL scale was observed for people treated with fingolimod or Avonex in the TRANSFORMS trial.	The Committee acknowledged that there was variation in current practice and therefore concluded that fingolimod should be compared with a weighted average of the comparators used in UK clinical practice of RRMS. That the most plausible ICER for fingolimod compared with the weighted average of the comparators was likely to be in the range of £25,000 to £35,000 per QALY gained from the main analysis on population 1b. In supplementary analyses For population 1b, excluding those who also met the criteria for population 2, the EAG concluded that the incremental analysis shows that in both populations Avonex is either dominated or extendedly dominated. The EAG therefore advised that the cost effectiveness of fingolimod should be derived from incremental analysis.

TA, year	Health states	Utilities & Costs	EAG key Criticism	Results
			Loss of treatment effectiveness – The Committee preferred a 50% waning of treatment effect after 5 years be included in the base-case analysis. **Unrealistic disability progression** – The Committee noted the concerns of the clinical specialists that the model may not reflect the natural history of multiple sclerosis, because it does not allow for improvement in EDSS scores. **Call for an economic model that reflects clinical practice in UK** - The Committee emphasised that it is important that a new model for multiple sclerosis is developed for any future appraisals of treatments for multiple sclerosis. The new model should ideally be based on UK patient cohorts, should use the best available evidence (including experience to date from the risk-sharing scheme) and should include all currently available treatments for multiple sclerosis, so that future appraisals of treatments for multiple sclerosis are directly relevant to UK clinical practice.	
TA127 (2007) (Tysabri, Biogen Inc.)[34]	21 in total: • 10 EDSS RRMS • 10 EDSS SPMS • Death	• RRMS EQ-5D EDSS 0-9, • SPMS Utility decrement • Caregiver disutilities • Relapse HS disutilities • AE utility decrements	**Uncertainty in the analysis on the population of interest -** The EAG was critical that the data for the comparators derived from people with RRMS rather than HA RRMS . The company excluded the SENTINEL trial SOT RRMS subgroup data from the model, especially that these was relied on for the marketing authorisation. **Loss of treatment effectiveness** – The EAG expressed concern about the extrapolation of 2-year data from the AFFIRM study to a 20-year time horizon.	The Committee noted that the base case ICERs estimated by the manufacturer for the suboptimal therapy group were £43,400 per QALY gained or higher. It therefore concluded that natalizumab would not be a cost-effective use of NHS resources in this group of people. The Committee concluded that the ICER of £32,000 per QALY for natalizumab compared with beta interferon presented by the manufacturer was more likely to be an overestimate. They concluded

TA, year	Health states	Utilities & Costs	EAG key Criticism	Results
		• Drug acquisition, administration and monitoring costs • HS Costs EDSS 0-9, • AE Costs	**Unrealistic disability progression** – the EAG expressed concern that, although the transition probabilities in the manufacturer's model were based on data from AFFIRM, the model appeared to predict a higher rate of sustained disability progression at 2 years than reported in AFFIRM. **Treatment effects on progression from RRMS to SPMS** – There wasn't evidence to support the assumption that Natalizumab reduces progression from RRMS to SPMS	natalizumab for the treatment of RES RRMS patients was a cost-effective use of NHS resources.

Abbreviations: **AE:** Adverse Events, **ARR:** Annualised Relapse Rate, **CDP**: Confirmed Disability Progression, EAG: External Assessment Group; **EDSS:** Expanded Disability Scale Status, **EQ-5D**: EuroQol five dimensions quality of life index, **GBP £:** Great Britain Pound, **HA RRMS:** Highly Active Relapse Remitting Multiple Sclerosis, **HDA RRMS:** High Disease Activity Relapse Remitting Multiple Sclerosis, **HS:** Health State, **ICER:** Incremental Cost-Effectiveness Ratio, **NHS:** National Health Service, **NMA:** Network Meta-Analysis, **QALY**: Quality Adjusted Life, **RES RRMS:** Rapidly Evolving Severe Relapse Remitting Multiple Sclerosis, **RRMS:** Relapse Remitting Multiple Sclerosis, **SAD**: Sustained Accumulation of Disability, **SOT RRMS:** Sub-Optimally Treated Relapse Remitting Multiple Sclerosis, **SPMS:** Secondary Progressive Multiple Sclerosis,

Appendix 7
Additional MS Registry results

Sample sizes for events in the MS registry are summarized in the tables Table 99 (those that depend on treatment) and

Table 100 (those that do not depend on treatment). The sample sizes for those that do not depend on treatment were considerably lower than for those that did depend on treatment, indicating that modelling their treatment dependence would result in poorly informed models.

Table 99 Samples sizes for events in the MS registry that were modelled to depend on treatment

Group	N	.Alemtuzumab	N.Beta.Interferon	N.Cladribine	N.Fingolimod	N.Glatiramer.Acetate	N.Natalizumab	N.Ocrelizumab	N.Ofatumumab	N.Ponesimod	N.Female
Time to EDSS Increase (RRMS Highly Active)	224	12	9	23	65	20	23	43	25	4	186
Time to EDSS Increase (All RRMS)	1016	41	168	35	158	158	177	203	69	7	838
Time to Relapse (RRMS Highly Active)	50	1	11	1	13	11	7	4	1	1	40
Time to Relapse (All RRMS)	191	9	56	2	34	44	28	15	2	1	150

Table 100 Samples sizes for events in the MS registry that were not modelled to depend on treatment

Group	N	N.Alemtuzumab	N.Beta.Interferon	N.Cladribine	N.Fingolimod	N.Glatiramer.Acetate	N.Natalizumab	N.Ocrelizumab	N.Ofatumumab	N.Ponesimod	N.Female
Time to EDSS Decrease (All RRMS)	793	29	159	12	93	138	156	160	43	3	652
Time to EDSS Increase (SPMS)	181	4	69	7	31	21	29	16	4	0	133
Time to Relapse (SPMS)	164	2	79	1	31	28	19	4	0	0	121
Time to SP Conversion (RRMS Highly Active)	66	2	23	0	20	14	3	4	0	0	46
Time to SP Conversion (All RRMS)	222	3	107	2	37	40	29	4	0	0	164

The covariance matrices for the coefficients (on log scale) of the exponential survival models estimated by the MS registry are reported below. These covariances were used when sampling the log rates used for the economic model, although only the coefficient for natalizumab was used from the DMT dependent models.

Table 101 Covariance matrix for coefficients of exponential survival model for Time to EDSS Increase (RRMS Highly Active)

	rate	EDSS	Alemtuzumab	Cladribine	Fingolimod	Glatiramer Acetate	Natalizumab	Ocrelizumab	Ofatumumab	Ponesimod
rate	0.26316339	-0.0188753	-0.2004151	-0.2160293	-0.2131976	-0.2207916	-0.2001307	-0.2067891	-0.1979965	-0.2045135
EDSS	-0.0188753	0.00564056	0.00012407	0.00479009	0.0039439	0.00621322	3.9063E-05	0.00202883	-0.0005987	0.00134879
Alemtuzumab	-0.2004151	0.00012407	0.34285982	0.20010533	0.20008672	0.20013663	0.20000083	0.20004459	0.1999868	0.20002964
Cladribine	-0.2160293	0.00479009	0.20010533	1.20406765	0.20334921	0.20527638	0.20003314	0.20172289	0.19949154	0.20114539
Fingolimod	-0.2131976	0.0039439	0.20008672	0.20334921	0.34561467	0.20434427	0.20002728	0.20141853	0.19958135	0.20094304
Glatiramer Acetate	-0.2207916	0.00621322	0.20013663	0.20527638	0.20434427	0.37351063	0.200043	0.20223477	0.19934048	0.20148569
Natalizumab	-0.2001307	3.9063E-05	0.20000083	0.20003314	0.20002728	0.200043	0.40000021	0.20001402	0.19999582	0.20000931
Ocrelizumab	-0.2067891	0.00202883	0.20004459	0.20172289	0.20141853	0.20223477	0.20001402	0.28406303	0.19978462	0.20048511
Ofatumumab	-0.1979965	-0.0005987	0.1999868	0.19949154	0.19958135	0.19934048	0.19999582	0.19978462	0.53339679	0.1998568
Ponesimod	-0.2045135	0.00134879	0.20002964	0.20114539	0.20094304	0.20148569	0.20000931	0.20048511	0.1998568	1.20032233

Table 102 Covariance matrix for coefficients of exponential survival model for Time to EDSS Increase (All RRMS)

	rate	EDSS	Alemtuzumab	Cladribine	Fingolimod	Glatiramer Acetate	Natalizumab	Ocrelizumab	Ofatumumab	Ponesimod
rate	0.0379168	-0.0042253	-0.0256477	-0.0264687	-0.0245772	-0.0253309	-0.0225739	-0.0250133	-0.024759	-0.0238234
EDSS	-0.0042253	0.00153897	-0.0002433	5.5707E-05	-0.0006332	-0.0003587	-0.0013629	-0.0004744	-0.000567	-0.0009078
Alemtuzumab	-0.0256477	-0.0002433	0.13746535	0.02630698	0.02641591	0.0263725	0.02653128	0.02639079	0.02640544	0.02645932
Cladribine	-0.0264687	5.5707E-05	0.02630698	0.35965108	0.02629286	0.0263028	0.02626645	0.02629861	0.02629526	0.02628292
Fingolimod	-0.0245772	-0.0006332	0.02641591	0.02629286	0.07005459	0.02646338	0.02687657	0.02651098	0.02654909	0.02668931
Glatiramer Acetate	-0.0253309	-0.0003587	0.0263725	0.0263028	0.02646338	0.06639939	0.02663346	0.02642636	0.02644795	0.02652738
Natalizumab	-0.0225739	-0.0013629	0.02653128	0.02626645	0.02687657	0.02663346	0.05191298	0.0267359	0.02681792	0.02711971
Ocrelizumab	-0.0250133	-0.0004744	0.02639079	0.02629861	0.02651098	0.02642636	0.0267359	0.04820114	0.02649057	0.02659561
Ofatumumab	-0.024759	-0.000567	0.02640544	0.02629526	0.02654909	0.02644795	0.02681792	0.02649057	0.12652468	0.02665025
Ponesimod	-0.0238234	-0.0009078	0.02645932	0.02628292	0.02668931	0.02652738	0.02711971	0.02659561	0.02665025	1.0268511

Table 103 Covariance matrix for coefficients of exponential survival model for Time to Relapse (RRMS Highly Active)

	rate	EDSS	Alemtuzumab	Cladribine	Fingolimod	Glatiramer Acetate	Natalizumab	Ocrelizumab	Ofatumumab	Ponesimod
rate	0.1760278	-0.0212619	-0.09098	-0.112242	-0.1078575	-0.1035607	-0.0569426	-0.0976834	-0.112242	-0.133504
EDSS	-0.0212619	0.00885927	-0.0141752	-0.0053159	-0.0071428	-0.0089332	-0.0283577	-0.0113821	-0.0053159	0.00354338
Alemtuzumab	-0.09098	-0.0141752	1.14768071	0.13350564	0.13642877	0.13929343	0.17037343	0.14321177	0.13350564	0.11933043
Cladribine	-0.112242	-0.0053159	0.13350564	1.12818956	0.12928594	0.13036023	0.14201567	0.13182966	0.12818972	0.12287382
Fingolimod	-0.1078575	-0.0071428	0.13642877	0.12928594	0.20768195	0.13220238	0.14786343	0.13417681	0.12928594	0.12214312
Glatiramer Acetate	-0.1035607	-0.0089332	0.13929343	0.13036023	0.13220238	0.24511877	0.15359423	0.13647701	0.13036023	0.12142704
Natalizumab	-0.0569426	-0.0283577	0.17037343	0.14201567	0.14786343	0.15359423	0.35862733	0.16143293	0.14201567	0.11365796
Ocrelizumab	-0.0976834	-0.0113821	0.14321177	0.13182966	0.13417681	0.13647701	0.16143293	0.38962324	0.13182966	0.12044757
Ofatumumab	-0.112242	-0.0053159	0.13350564	0.12818972	0.12928594	0.13036023	0.14201567	0.13182966	1.12818956	0.12287382
Ponesimod	-0.133504	0.00354338	0.11933043	0.12287382	0.12214312	0.12142704	0.11365796	0.12044757	0.12287382	1.12641703

Table 104 Covariance matrix for coefficients of exponential survival model for Time to Relapse (All RRMS)

	rate	EDSS	Alemtuzumab	Cladribine	Fingolimod	Glatiramer Acetate	Natalizumab	Ocrelizumab	Ofatumumab	Ponesimod
rate	0.0531041	-0.0074094	-0.0248499	-0.0294932	-0.0219009	-0.0251326	-0.0169087	-0.0198371	-0.0335028	-0.0382852
EDSS	-0.0074094	0.00191196	0.0001186	0.0013168	-0.0006423	0.00019157	-0.0019306	-0.0011749	0.00235144	0.00358552
Alemtuzumab	-0.0248499	0.0001186	0.14939758	0.02447193	0.02435039	0.02440212	0.02427048	0.02431736	0.02453611	0.02461266
Cladribine	-0.0294932	0.0013168	0.02447193	0.52529706	0.02394784	0.02452217	0.02306063	0.02358107	0.02600972	0.02685964
Fingolimod	-0.0219009	-0.0006423	0.02435039	0.02394784	0.05686411	0.02432588	0.02503884	0.02478496	0.02360024	0.02318564
Glatiramer Acetate	-0.0251326	0.00019157	0.02440212	0.02452217	0.02432588	0.04940943	0.02419681	0.02427252	0.02462584	0.02474949
Natalizumab	-0.0169087	-0.0019306	0.02427048	0.02306063	0.02503884	0.02419681	0.06480111	0.02557657	0.02201592	0.02076985
Ocrelizumab	-0.0198371	-0.0011749	0.02431736	0.02358107	0.02478496	0.02427252	0.02557657	0.10844554	0.02294528	0.02218694
Ofatumumab	-0.0335028	0.00235144	0.02453611	0.02600972	0.02360024	0.02462584	0.02201592	0.02294528	0.52728212	0.02879993

Ponesimod	-0.0382852	0.00358552	0.02461266	0.02685964	0.02318564	0.02474949	0.02076985	0.02218694	0.02879993	1.03111405

Table 105 Covariance matrix for coefficients of exponential survival model for Time to EDSS Decrease (All RRMS)

	rate	EDSS
rate	0.048537	-0.0099457
EDSS	-0.0099457	0.00242531

Table 106 Covariance matrix for coefficients of exponential survival model for Time to EDSS Increase (SPMS)

	rate	**EDSS**
rate	0.41327905	-0.0685228
EDSS	-0.0685228	0.01220504

Table 107 Covariance matrix for coefficients of exponential survival model for Time to Relapse (SPMS)

	rate	**EDSS**
rate	0.86895777	-0.1357356
EDSS	-0.1357356	0.02188323

Table 108 Covariance matrix for coefficients of exponential survival model for Time to SP Conversion (RRMS Highly Active)

	rate	**EDSS**
rate	0.45009625	-0.0734639
EDSS	-0.0734639	0.01242186

Table 109 Covariance matrix for coefficients of exponential survival model for Time to SP Conversion (All RRMS)

	rate	**EDSS**
rate	0.13046351	-0.0207383
EDSS	-0.0207383	0.0034233

The results of fitting the multistate model to the All RRMS population are provided in Table 110 with standard errors in Table 111.

Table 110 MS registry log rates of transition between EDSS states based on multistate model

	0	1	2	3	4	5	6	7	8
0	0	5.33192944	0	0	0	0	0	0	0
1	6.21287963	0	2.06546476	0	0	0	0	0	0
2	0	-0.714375	0	3.94007716	0	0	0	0	0
3	0	0	3.89699664	0	-0.3884832	0	0	0	0
4	0	0	0	-0.3449541	0	0.16070213	0	0	0
5	0	0	0	0	0.59315005	0	0.31408698	0	0
6	0	0	0	0	0	-1.191966	0	-1.9983354	0
7	0	0	0	0	0	0	-1.1958821	0	-1.4518141
8	0	0	0	0	0	0	0	1.25944346	0

Table 111 Standard errors for MS registry log rates of transition between EDSS states based on multistate model

	0	1	2	3	4	5	6	7	8
0	0	2.10122434	0	0	0	0	0	0	0
1	2.08691526	0	0.345469	0	0	0	0	0	0
2	0	0.30187187	0	1.61466577	0	0	0	0	0
3	0	0	1.61681602	0	0.1488902	0	0	0	0
4	0	0	0	0.16046662	0	0.17763808	0	0	0
5	0	0	0	0	0.19043778	0	0.16388654	0	0
6	0	0	0	0	0	0.15350255	0	0.16672652	0
7	0	0	0	0	0	0	0.20999212	0	0.70836177
8	0	0	0	0	0	0	0	0.78283474	0

Appendix 8
Additional economic results

The total costs, total QALYs, and net benefits from the sensitivity analyses are presented below.

Table 112 Costs, QALYs and Net Benefit for treatments in comparison to Natalizumab IV (publicly available list prices) for Scenario 1 (All RRMS MS Registry population)

Treatment	Total costs (95% CrI)	Total QALYs (95% CrI)	Net benefit at £20,000/QALY (95% CrI)	Net benefit at £30,000/QALY (95% CrI)
Natalizumab-IV	334844.87 (300376.37, 379984.55)	8.10 (6.08, 10.13)	-172801.54 (-211919.50, -130541.88)	-91779.87 (-139808.06, -33136.28)
Natalizumab-SC	336991.91 (298531.26, 384330.38)	8.15 (6.23, 10.25)	-173977.20 (-223000.00, -129570.70)	-92469.84 (-154717.88, -31105.50)
Natalizumab biosimilar-IV	325930.41 (294654.09, 378573.07)	8.13 (6.58, 10.37)	-163302.48 (-215388.78, -113055.19)	-81988.51 (-147293.35, -13587.19)
Natalizumab biosimilar-SC	314237.29 (281120.44, 359466.35)	7.97 (6.16, 10.12)	-154783.00 (-192756.64, -111100.77)	-75055.85 (-124404.87, -13489.28)
Fingolimod	291932.13 (262808.03, 325500.59)	8.19 (6.33, 10.59)	-128053.62 (-183923.87, -82883.15)	-46114.36 (-118841.18, 17538.94)
Alemtuzumab	271790.68 (242889.02, 313272.12)	7.75 (6.09, 9.85)	-116846.22 (-171483.74, -77190.23)	-39374.00 (-102936.83, 19318.27)
Cladribine	278758.49 (249323.03, 322258.44)	7.87 (6.15, 9.92)	-121298.08 (-165876.49, -74490.69)	-42567.87 (-102893.54, 21914.15)
Ponesimod	323946.94 (289387.20, 370169.94)	8.14 (6.20, 10.27)	-161117.84 (-205603.68, -117047.78)	-79703.29 (-136416.64, -23400.53)
Ofatumumab	336364.40 (298310.10, 391625.01)	8.20 (6.69, 10.22)	-172287.51 (-214249.44, -119392.49)	-90249.06 (-144733.14, -22783.49)
Ocrelizumab	238541.53 (216480.60, 268583.28)	8.04 (6.34, 10.01)	-77678.31 (-122742.11, -32456.56)	2753.30 (-53838.79, 65407.22)
Peginterferon-beta-1 SC 125µg	249092.45 (224915.21, 286230.96)	7.92 (6.18, 9.99)	-90721.95 (-138542.10, -45550.74)	-11536.71 (-75823.24, 52523.81)
Interferon-beta-1a SC 22µg	236928.45 (213020.13, 276878.77)	7.94 (5.82, 10.08)	-78128.20 (-124572.17, -37693.17)	1271.92 (-63252.91, 57529.82)
Interferon-beta-1a SC 44µg	240637.44 (215965.78, 275556.28)	7.93 (6.35, 10.14)	-81972.10 (-125481.79, -32849.51)	-2639.43 (-62946.71, 63727.30)

Treatment	Total costs (95% CrI)	Total QALYs (95% CrI)	Net benefit at £20,000/QALY (95% CrI)	Net benefit at £30,000/QALY (95% CrI)
Interferon-beta-1a IM 30µg	231839.40 (204378.29, 276631.36)	8.29 (6.47, 10.74)	-65972.89 (-112325.18, -16250.74)	16960.36 (-42013.01, 88235.91)
Interferon-beta-1b SC 250µg	228984.90 (202085.77, 259044.91)	7.95 (6.42, 10.36)	-69941.46 (-114012.97, -25548.24)	9580.25 (-45444.03, 78080.68)
Glatiramer Acetate 20mg	229240.29 (203414.10, 268889.37)	7.97 (6.08, 10.17)	-69824.93 (-117248.14, -24823.12)	9882.75 (-53911.76, 70002.81)
Glatiramer Acetate 40mg	334844.87 (300376.37, 379984.55)	8.10 (6.08, 10.13)	-172801.54 (-211919.50, -130541.88)	-91779.87 (-139808.06, -33136.28)

Table 113 Costs, QALYs and Net Benefit for treatments in comparison to Natalizumab IV (publicly available list prices) for Scenario 2 (base-case w/ random effects NMA)

Treatment	Total costs (95% CrI)	Total QALYs (95% CrI)	Net benefit at £20,000/QALY (95% CrI)	Net benefit at £30,000/QALY (95% CrI)
Natalizumab-IV	335457.12 (286290.85, 396815.35)	9.06 (7.28, 11.37)	-154341.40 (-201095.14, -99281.19)	-63783.54 (-120860.96, 7654.02)
Natalizumab-SC	334493.57 (282401.54, 394123.71)	9.08 (6.96, 11.29)	-152981.96 (-205138.45, -104523.96)	-62226.16 (-130576.02, 2901.63)
Natalizumab biosimilar-IV	328155.36 (284094.46, 394393.63)	9.05 (7.21, 11.58)	-147239.09 (-199900.61, -89999.60)	-56780.96 (-119668.10, 21038.75)
Natalizumab biosimilar-SC	316632.11 (279622.02, 373768.81)	9.11 (7.11, 11.89)	-134416.84 (-177871.59, -84459.89)	-43309.21 (-95726.86, 25841.83)
Fingolimod	284957.20 (254325.38, 329804.38)	8.88 (5.95, 11.57)	-107385.91 (-196635.10, -52502.50)	-18600.27 (-124029.70, 58252.74)
Alemtuzumab	261628.55 (229698.02, 301771.86)	8.97 (7.21, 11.34)	-82315.99 (-146274.72, -38400.15)	7340.29 (-67758.23, 66593.64)
Cladribine	275845.50 (241654.26, 318649.85)	8.82 (6.39, 11.18)	-99522.24 (-148353.37, -58464.48)	-11360.61 (-84429.77, 48764.18)
Ponesimod	326446.24 (284024.46, 384292.64)	8.81 (6.24, 11.48)	-150156.94 (-195130.89, -101080.63)	-62012.30 (-128052.50, -5494.78)
Ofatumumab	338953.85 (287291.02, 396719.63)	9.03 (6.81, 11.36)	-158451.58 (-215935.09, -105902.68)	-68200.45 (-133826.50, -2990.48)
Ocrelizumab	227087.94 (202729.53, 272457.97)	9.81 (7.98, 12.12)	-30889.02 (-74014.90, 7298.15)	67210.44 (4886.11, 122109.89)
Peginterferon-beta-1 SC 125µg	242025.05 (218389.01, 278536.01)	8.72 (5.95, 11.11)	-67548.58 (-129116.56, -20239.73)	19689.65 (-72340.81, 87682.79)

Treatment	Total costs (95% CrI)	Total QALYs (95% CrI)	Net benefit at £20,000/QALY (95% CrI)	Net benefit at £30,000/QALY (95% CrI)
Interferon-beta-1a SC 22µg	230149.75 (203857.60, 269319.45)	8.65 (6.13, 11.31)	-57086.17 (-114352.20, 2541.99)	29445.62 (-53524.88, 116044.26)
Interferon-beta-1a SC 44µg	233080.15 (208074.10, 265937.40)	8.89 (6.74, 11.60)	-55265.79 (-123606.60, -3199.64)	33641.39 (-52369.05, 108708.44)
Interferon-beta-1a IM 30µg	225465.84 (199630.56, 268789.96)	9.11 (6.47, 11.72)	-43298.58 (-115625.26, 1494.94)	47785.05 (-40236.55, 114276.46)
Interferon-beta-1b SC 250µg	223618.25 (197932.77, 265094.37)	8.88 (6.14, 11.53)	-46117.28 (-120149.15, 10616.90)	42633.20 (-54385.86, 123245.51)
Glatiramer Acetate 20mg	224569.88 (196670.47, 259792.05)	8.84 (6.92, 11.36)	-47712.20 (-106642.54, 5415.00)	40716.64 (-43128.85, 115680.66)
Glatiramer Acetate 40mg	335457.12 (286290.85, 396815.35)	9.06 (7.28, 11.37)	-154341.40 (-201095.14, -99281.19)	-63783.54 (-120860.96, 7654.02)

Table 114 Costs, QALYs and Net Benefit for treatments in comparison to Natalizumab IV (publicly available list prices) for Scenario 3 (base-case & assuming JCV testing provided free of charge by manufacturers)

Treatment	Total costs (95% CrI)	Total QALYs (95% CrI)	Net benefit at £20,000/QALY (95% CrI)	Net benefit at £30,000/QALY (95% CrI)
Natalizumab-IV	334292.58 (283914.88, 397946.59)	9.00 (6.66, 11.44)	-154267.74 (-210122.34, -92816.20)	-64255.33 (-140311.16, 10300.89)
Natalizumab-SC	334045.86 (284606.79, 405206.25)	9.04 (6.79, 11.57)	-153147.75 (-210144.98, -102539.39)	-62698.69 (-125050.98, 3230.00)
Natalizumab biosimilar-IV	327339.94 (284394.35, 383750.19)	9.01 (6.99, 11.64)	-147187.90 (-198417.78, -91744.71)	-57111.89 (-119090.54, 14937.18)
Natalizumab biosimilar-SC	314433.77 (276943.82, 372570.57)	8.92 (7.01, 11.45)	-136085.91 (-181558.91, -88479.07)	-46911.98 (-119830.43, 18599.97)
Fingolimod	284200.95 (247918.58, 326044.63)	9.12 (6.76, 11.61)	-101802.29 (-186117.87, -46248.17)	-10602.96 (-112175.94, 67950.68)
Alemtuzumab	262681.07 (232396.85, 313506.69)	8.83 (6.64, 11.45)	-86064.65 (-148434.56, -29815.62)	2243.57 (-81162.53, 78095.37)
Cladribine	276922.06 (243190.86, 316573.16)	8.92 (6.92, 11.41)	-98597.42 (-151947.87, -43702.10)	-9435.10 (-85413.78, 66678.28)
Ponesimod	325522.52 (277499.59, 387091.04)	9.01 (6.80, 11.77)	-145289.12 (-206115.81, -91540.31)	-55172.42 (-131742.36, 21786.81)

Treatment	Total costs (95% CrI)	Total QALYs (95% CrI)	Net benefit at £20,000/QALY (95% CrI)	Net benefit at £30,000/QALY (95% CrI)
Ofatumumab	340572.61 (285842.98, 412929.22)	9.09 (7.36, 11.45)	-158720.02 (-214264.34, -105170.20)	-67793.73 (-127592.33, -3961.78)
Ocrelizumab	233006.23 (209358.07, 274820.28)	8.94 (7.01, 11.53)	-54130.05 (-113880.18, -8883.89)	35308.04 (-42977.85, 104136.52)
Peginterferon-beta-1 SC 125µg	243231.91 (218742.37, 278511.16)	8.95 (6.77, 11.68)	-64183.62 (-126026.91, -11521.83)	25340.52 (-65933.25, 103150.58)
Interferon-beta-1a SC 22µg	230182.04 (207818.42, 262164.55)	8.92 (6.63, 11.52)	-51808.55 (-118308.81, -1786.81)	37378.19 (-51345.28, 111859.51)
Interferon-beta-1a SC 44µg	232627.45 (207960.01, 272552.25)	8.85 (6.07, 11.34)	-55709.01 (-124240.48, -3887.46)	32750.21 (-57382.07, 105167.33)
Interferon-beta-1a IM 30µg	226364.34 (195757.54, 264850.42)	9.23 (7.13, 11.58)	-41812.19 (-97880.73, 3751.42)	50463.89 (-32031.57, 111520.95)
Interferon-beta-1b SC 250µg	224563.19 (198677.28, 270438.73)	8.88 (6.52, 11.60)	-46866.14 (-115166.46, 15782.92)	41982.39 (-44783.64, 130661.11)
Glatiramer Acetate 20mg	225333.76 (201571.28, 255982.79)	8.93 (6.77, 11.40)	-46739.87 (-104445.54, 805.92)	42557.07 (-27078.64, 117633.90)
Glatiramer Acetate 40mg	334292.58 (283914.88, 397946.59)	9.00 (6.66, 11.44)	-154267.74 (-210122.34, -92816.20)	-64255.33 (-140311.16, 10300.89)

Table 115 Costs, QALYs and Net Benefit for treatments in comparison to Natalizumab IV (publicly available list prices) for Scenario 4 (base-case & assuming lowest generic prices)

Treatment	Total costs (95% CrI)	Total QALYs (95% CrI)	Net benefit at £20,000/QALY (95% CrI)	Net benefit at £30,000/QALY (95% CrI)
Natalizumab-IV	440861.06 (378263.38, 513787.22)	11.16 (8.33, 14.61)	-217607.39 (-315129.16, -135605.66)	-105980.56 (-233550.74, -2028.30)
Natalizumab-SC	443081.63 (382050.84, 529808.59)	11.09 (8.16, 14.73)	-221188.31 (-335527.14, -136028.28)	-110241.65 (-251929.07, 2762.27)
Natalizumab biosimilar-IV	430673.57 (373847.46, 520422.47)	11.14 (8.25, 14.66)	-207888.49 (-307430.55, -130966.78)	-96495.95 (-224323.29, 10421.14)
Natalizumab biosimilar-SC	321004.97 (286751.31, 389655.37)	11.07 (7.75, 14.28)	-99565.27 (-218089.12, -35206.36)	11154.58 (-137715.34, 102992.38)
Fingolimod	374553.80 (333000.78, 448691.97)	11.24 (7.91, 14.76)	-149685.80 (-276104.48, -72705.60)	-37251.80 (-192083.69, 73022.30)

Treatment	Total costs (95% CrI)	Total QALYs (95% CrI)	Net benefit at £20,000/QALY (95% CrI)	Net benefit at £30,000/QALY (95% CrI)
Alemtuzumab	360761.71 (318416.75, 425363.70)	10.73 (7.44, 14.04)	-146252.05 (-269550.95, -65342.29)	-38997.22 (-192832.75, 72381.86)
Cladribine	379234.33 (331362.45, 454133.39)	10.86 (7.73, 14.33)	-161978.72 (-283138.57, -87138.64)	-53350.91 (-214848.78, 51649.92)
Ponesimod	432340.84 (372382.90, 523177.89)	11.09 (7.79, 14.23)	-210585.50 (-346935.22, -128713.93)	-99707.84 (-260404.69, 200.50)
Ofatumumab	443716.05 (380070.92, 531391.23)	11.16 (7.80, 14.35)	-220535.94 (-329387.53, -134966.92)	-108945.89 (-257357.67, -4182.70)
Ocrelizumab	323507.65 (282999.71, 390027.63)	11.15 (8.23, 14.48)	-100577.20 (-202121.80, -16587.71)	10888.03 (-121943.39, 123555.36)
Peginterferon-beta-1 SC 125µg	340088.45 (300531.95, 412241.84)	10.88 (7.61, 14.40)	-122520.82 (-255598.58, -37766.61)	-13737.00 (-187523.58, 99365.92)
Interferon-beta-1a SC 22µg	325186.24 (282079.90, 399676.76)	10.96 (7.59, 14.55)	-105918.82 (-215831.14, -17551.16)	3714.89 (-143181.47, 126723.92)
Interferon-beta-1a SC 44µg	328592.86 (289311.69, 407580.90)	10.83 (7.56, 14.04)	-111951.63 (-244211.26, -32344.03)	-3631.02 (-162567.02, 103143.42)
Interferon-beta-1a IM 30µg	314158.86 (272701.38, 387288.81)	11.39 (7.90, 14.83)	-86414.69 (-199568.58, -7326.18)	27457.39 (-122515.69, 137099.17)
Interferon-beta-1b SC 250µg	315053.79 (272543.07, 393852.69)	10.91 (7.25, 14.31)	-96795.23 (-233350.88, -23112.98)	12334.05 (-165595.06, 114496.71)
Glatiramer Acetate 20mg	314423.17 (274590.61, 382561.78)	11.05 (7.85, 14.85)	-93464.83 (-220578.09, -13133.79)	17014.34 (-139041.33, 126338.30)
Glatiramer Acetate 40mg	440861.06 (378263.38, 513787.22)	11.16 (8.33, 14.61)	-217607.39 (-315129.16, -135605.66)	-105980.56 (-233550.74, -2028.30)

Table 116 Costs, QALYs and Net Benefit for treatments in comparison to Natalizumab IV (publicly available list prices) for Scenario 5 (base case & assuming a reduction in Natalizumab-SC administration costs)

Treatment	Total costs (95% CrI)	Total QALYs (95% CrI)	Net benefit at £20,000/QALY (95% CrI)	Net benefit at £30,000/QALY (95% CrI)
Natalizumab-IV	334869.97 (284660.24, 398385.10)	9.00 (6.66, 11.44)	-154845.13 (-210387.75, -93764.52)	-64832.71 (-140679.51, 9767.06)
Natalizumab-SC	308379.27 (268436.60, 367248.84)	9.04 (6.79, 11.57)	-127481.15 (-177587.31, -80833.33)	-37032.10 (-104747.42, 23281.96)
Natalizumab biosimilar-IV	326199.93 (284127.33, 381833.98)	9.01 (6.99, 11.64)	-146047.89 (-197418.73, -90718.35)	-55971.88 (-117602.32, 15610.31)
Natalizumab biosimilar-SC	313287.67 (276429.94, 371945.25)	8.92 (7.01, 11.45)	-134939.81 (-181130.87, -87359.61)	-45765.88 (-119460.24, 19751.55)
Fingolimod	283203.68 (245893.25, 325902.57)	9.12 (6.76, 11.61)	-100805.02 (-185967.82, -44654.59)	-9605.69 (-112125.83, 69019.40)
Alemtuzumab	261559.26 (231123.49, 312803.87)	8.83 (6.64, 11.45)	-84942.83 (-148216.48, -28256.10)	3365.38 (-80564.38, 79711.12)
Cladribine	275836.37 (242645.88, 315098.27)	8.92 (6.92, 11.41)	-97511.73 (-151558.97, -43059.30)	-8349.41 (-84989.43, 67277.77)
Ponesimod	324536.59 (277039.93, 384953.47)	9.01 (6.80, 11.77)	-144303.19 (-205074.40, -90665.94)	-54186.49 (-130661.49, 22942.00)
Ofatumumab	339563.62 (285670.02, 410541.34)	9.09 (7.36, 11.45)	-157711.03 (-212708.05, -105038.99)	-66784.74 (-126253.99, -2482.01)
Ocrelizumab	231939.94 (207727.36, 273468.39)	8.94 (7.01, 11.53)	-53063.76 (-112752.32, -7499.09)	36374.33 (-42334.65, 105677.16)
Peginterferon-beta-1 SC 125µg	242182.39 (217492.28, 277914.13)	8.95 (6.77, 11.68)	-63134.11 (-125991.97, -9810.15)	26390.03 (-65545.42, 105427.88)
Interferon-beta-1a SC 22µg	229190.54 (206965.70, 261468.47)	8.92 (6.63, 11.52)	-50817.05 (-117868.17, -93.12)	38369.69 (-50700.60, 113755.57)
Interferon-beta-1a SC 44µg	231621.53 (206970.43, 271639.39)	8.85 (6.07, 11.34)	-54703.09 (-123958.24, -2681.66)	33756.13 (-56813.01, 106338.23)
Interferon-beta-1a IM 30µg	225297.16 (194745.35, 263890.47)	9.23 (7.13, 11.58)	-40745.01 (-97419.41, 4881.46)	51531.07 (-31104.56, 112675.55)
Interferon-beta-1b SC 250µg	223562.48 (197643.98, 269068.74)	8.88 (6.52, 11.60)	-45865.43 (-114705.33, 16895.73)	42983.10 (-44281.79, 131840.08)
Glatiramer Acetate 20mg	224245.64 (200499.05, 255816.05)	8.93 (6.77, 11.40)	-45651.75 (-103548.73, 2533.68)	43645.19 (-26618.62, 119310.89)

Treatment	Total costs (95% CrI)	Total QALYs (95% CrI)	Net benefit at £20,000/QALY (95% CrI)	Net benefit at £30,000/QALY (95% CrI)
Glatiramer Acetate 40mg	334869.97 (284660.24, 398385.10)	9.00 (6.66, 11.44)	-154845.13 (-210387.75, -93764.52)	-64832.71 (-140679.51, 9767.06)

Table 117 Costs, QALYs and Net Benefit for treatments in comparison to Natalizumab IV (publicly available list prices) for Scenario 6 (base-case w/ HA RRMS fixed effects NMA)

Treatment	Total costs (95% CrI)	Total QALYs (95% CrI)	Net benefit at £20,000/QALY (95% CrI)	Net benefit at £30,000/QALY (95% CrI)
Natalizumab-IV	336522.11 (285045.75, 403408.28)	8.98 (6.86, 11.44)	-156844.72 (-205822.60, -98613.23)	-67006.02 (-124560.90, 5133.64)
Natalizumab-SC	335585.21 (291999.65, 400241.43)	9.14 (6.84, 11.56)	-152818.81 (-212701.38, -101402.22)	-61435.61 (-141362.77, 7113.67)
Natalizumab biosimilar-IV	325600.14 (281569.32, 382401.22)	9.15 (7.09, 11.44)	-142674.20 (-190719.41, -95050.44)	-51211.23 (-121827.63, 13921.60)
Natalizumab biosimilar-SC	316365.08 (277301.94, 366978.70)	8.98 (6.68, 11.46)	-136786.36 (-184213.55, -79420.98)	-46997.00 (-115745.92, 32178.09)
Fingolimod	284999.28 (256274.46, 320460.15)	9.09 (6.91, 11.60)	-103286.34 (-169391.59, -46392.80)	-12429.87 (-93061.38, 70595.29)
Alemtuzumab	262487.36 (231120.60, 301928.47)	8.85 (6.62, 11.61)	-85422.31 (-157253.69, -28045.91)	3110.21 (-83223.03, 88180.93)
Cladribine	276016.05 (245005.69, 322497.69)	8.96 (6.90, 11.74)	-96790.70 (-145456.26, -52096.91)	-7178.03 (-71741.26, 56247.74)
Ponesimod	325583.04 (280842.04, 391728.22)	9.06 (6.84, 11.52)	-144391.94 (-204874.84, -92172.63)	-53796.40 (-127013.45, 11958.44)
Ofatumumab	340014.06 (287878.34, 412347.15)	9.16 (7.20, 11.50)	-156819.43 (-212269.65, -102073.59)	-65222.11 (-135730.80, 7661.89)
Ocrelizumab	232318.87 (205984.51, 272685.55)	9.06 (6.95, 11.62)	-51099.59 (-121317.84, -5323.01)	39510.06 (-53902.40, 107696.63)
Peginterferon-beta-1 SC 125µg	240898.43 (217529.08, 277773.52)	9.03 (6.84, 11.71)	-60383.49 (-118386.02, -18564.64)	29873.98 (-43266.20, 91839.90)
Interferon-beta-1a SC 22µg	228959.48 (203648.79, 268608.47)	8.99 (6.56, 11.60)	-49227.11 (-112429.45, 2062.25)	40639.07 (-43933.91, 114609.49)

Treatment	Total costs (95% CrI)	Total QALYs (95% CrI)	Net benefit at £20,000/QALY (95% CrI)	Net benefit at £30,000/QALY (95% CrI)
Interferon-beta-1a SC 44µg	232797.94 (204460.85, 265045.85)	8.96 (6.38, 11.57)	-53644.10 (-119317.19, -880.75)	35932.82 (-60394.43, 109989.29)
Interferon-beta-1a IM 30µg	223874.13 (199174.98, 257881.23)	9.17 (7.09, 11.80)	-40409.96 (-113687.17, 8237.79)	51322.13 (-32727.17, 119661.33)
Interferon-beta-1b SC 250µg	222446.73 (190719.11, 264206.13)	8.92 (6.83, 11.67)	-44001.87 (-106128.93, 9074.42)	45220.55 (-33753.96, 123165.28)
Glatiramer Acetate 20mg	223628.73 (196429.92, 266731.51)	8.95 (6.75, 11.35)	-44681.17 (-105527.20, -2336.23)	44792.61 (-29528.28, 104057.40)
Glatiramer Acetate 40mg	336522.11 (285045.75, 403408.28)	8.98 (6.86, 11.44)	-156844.72 (-205822.60, -98613.23)	-67006.02 (-124560.90, 5133.64)

Table 118 Costs, QALYs and Net Benefit for treatments in comparison to Natalizumab IV (publicly available list prices) for Scenario 7 (mortality by severity Sadovnik et al cited in Pokorski et al)

Treatment	Total costs (95% CrI)	Total QALYs (95% CrI)	Net benefit at £20,000/QALY (95% CrI)	Net benefit at £30,000/QALY (95% CrI)
Natalizumab-IV	334975.89 (282422.63, 413519.56)	9.11 (6.83, 11.55)	-152729.95 (-200351.11, -100105.77)	-61606.98 (-119789.80, 5682.57)
Natalizumab-SC	336307.31 (288396.40, 402173.68)	9.04 (6.52, 11.52)	-155504.51 (-216281.49, -90843.76)	-65103.12 (-147082.69, 13171.69)
Natalizumab biosimilar-IV	325471.39 (283398.58, 389723.90)	8.96 (6.62, 11.19)	-146236.14 (-198015.59, -89508.69)	-56618.52 (-122969.99, 17417.18)
Natalizumab biosimilar-SC	314259.14 (276983.17, 368873.60)	8.86 (7.02, 11.41)	-137130.88 (-184093.61, -92451.07)	-48566.76 (-107778.51, 17335.24)
Fingolimod	283276.00 (252731.46, 320933.88)	9.07 (6.89, 11.54)	-101777.90 (-159649.60, -50824.87)	-11028.85 (-87192.89, 58182.71)
Alemtuzumab	260923.43 (226045.36, 307859.71)	8.75 (6.40, 11.47)	-85991.11 (-153506.35, -32528.63)	1475.06 (-88424.27, 76394.68)
Cladribine	275658.53 (246384.90, 314180.68)	8.89 (6.90, 11.55)	-97890.82 (-152048.05, -54067.89)	-9006.96 (-83806.67, 59282.41)
Ponesimod	324945.82 (277390.26, 387016.91)	8.93 (6.58, 11.37)	-146248.37 (-210329.93, -87589.23)	-56899.65 (-133128.43, 17587.20)
Ofatumumab	337551.25 (287716.94, 405417.46)	9.18 (7.08, 11.39)	-153905.65 (-210815.42, -92907.46)	-62082.85 (-125034.07, 15679.61)
Ocrelizumab	232096.31 (206525.39, 264328.67)	8.98 (6.60, 11.40)	-52430.17 (-113780.16, -12631.50)	37402.90 (-48826.09, 92384.83)
Peginterferon-beta-1 SC 125µg	241236.09 (218689.60, 280568.40)	8.89 (6.76, 11.13)	-63397.91 (-128393.94, -19636.07)	25521.19 (-59548.11, 86557.99)
Interferon-beta-1a SC 22µg	229933.38 (202049.81, 258857.08)	8.90 (6.60, 11.41)	-51898.26 (-106381.88, -2029.99)	37119.30 (-36450.66, 108440.39)
Interferon-beta-1a SC 44µg	232410.32 (208664.36, 273420.50)	8.80 (6.25, 11.43)	-56478.09 (-126306.83, -4371.70)	31488.03 (-61947.35, 103864.31)
Interferon-beta-1a IM 30µg	223445.57 (198701.80, 260421.19)	9.25 (7.04, 11.36)	-38493.03 (-99058.82, 5959.25)	53983.24 (-27594.66, 116769.21)
Interferon-beta-1b SC 250µg	223563.23 (200667.46, 274626.01)	8.88 (6.72, 11.74)	-45942.76 (-112631.26, 5210.68)	42867.47 (-44172.20, 116788.61)

Treatment	Total costs (95% CrI)	Total QALYs (95% CrI)	Net benefit at £20,000/QALY (95% CrI)	Net benefit at £30,000/QALY (95% CrI)
Glatiramer Acetate 20mg	223174.34 (194865.59, 265314.45)	8.96 (6.80, 11.63)	-44009.50 (-105585.60, 3924.33)	45572.92 (-31371.79, 114548.94)
Glatiramer Acetate 40mg	334975.89 (282422.63, 413519.56)	9.11 (6.83, 11.55)	-152729.95 (-200351.11, -100105.77)	-61606.98 (-119789.80, 5682.57)

Table 119 Costs, QALYs and Net Benefit for treatments in comparison to Natalizumab IV (publicly available list prices) for Scenario 8 (clinical equivalence: natalizumab and natalizumab biosimilar)

Treatment	Total costs (95% CrI)	Total QALYs (95% CrI)	Net benefit at £20,000/QALY (95% CrI)	Net benefit at £30,000/QALY (95% CrI)
Natalizumab-IV	337478.58 (282825.09, 405125.50)	9.08 (6.80, 11.39)	-155811.32 (-212750.43, -99481.56)	-64977.69 (-128740.27, 1804.04)
Natalizumab-SC	336789.66 (285699.54, 393520.22)	8.99 (6.78, 11.72)	-157089.50 (-205448.87, -102594.97)	-67239.42 (-134822.56, 5134.86)
Natalizumab biosimilar-IV	327417.97 (284744.83, 391187.75)	9.08 (6.84, 11.57)	-145791.80 (-203845.76, -93814.66)	-54978.72 (-137911.95, 15932.24)
Natalizumab biosimilar-SC	317114.05 (278467.28, 375123.94)	8.93 (6.72, 11.72)	-138474.34 (-200077.83, -86571.11)	-49154.49 (-142047.74, 23056.10)
Fingolimod	284502.20 (253364.78, 319893.79)	9.14 (7.16, 11.50)	-101662.88 (-167619.69, -44271.27)	-10243.23 (-92752.49, 65724.57)
Alemtuzumab	262833.68 (226938.87, 304120.02)	8.81 (6.59, 11.64)	-86631.60 (-152653.93, -21468.64)	1469.44 (-81561.95, 92519.77)
Cladribine	277298.15 (245414.85, 324022.40)	8.91 (6.52, 11.67)	-99126.09 (-158394.39, -47904.53)	-10040.06 (-91247.16, 61157.77)
Ponesimod	327246.56 (281670.46, 387589.26)	9.12 (6.95, 11.37)	-144779.96 (-196683.86, -95798.33)	-53546.66 (-122194.97, 4895.62)
Ofatumumab	339612.57 (290697.11, 414959.02)	9.05 (6.89, 11.40)	-158678.80 (-214127.41, -104092.68)	-68211.92 (-135975.17, -2199.41)
Ocrelizumab	231655.17 (205483.94, 265032.29)	9.07 (6.68, 11.68)	-50233.41 (-108525.89, -995.39)	40477.48 (-38384.64, 112572.29)
Peginterferon-beta-1 SC 125µg	242690.39 (217207.62, 288817.47)	8.90 (6.59, 11.32)	-64731.95 (-134345.10, -18950.75)	24247.27 (-69283.74, 90113.05)

Treatment	Total costs (95% CrI)	Total QALYs (95% CrI)	Net benefit at £20,000/QALY (95% CrI)	Net benefit at £30,000/QALY (95% CrI)
Interferon-beta-1a SC 22µg	229975.74 (206477.65, 270053.63)	8.86 (6.64, 11.23)	-52766.94 (-117420.92, -5360.76)	35837.46 (-45030.60, 103564.82)
Interferon-beta-1a SC 44µg	233663.77 (202683.71, 275359.26)	8.95 (6.72, 11.61)	-54739.49 (-114076.99, -3142.50)	34722.65 (-43534.14, 109402.21)
Interferon-beta-1a IM 30µg	225667.77 (202653.53, 263022.71)	9.12 (6.53, 11.52)	-43218.47 (-114060.60, 9285.12)	48006.18 (-41890.80, 122281.09)
Interferon-beta-1b SC 250µg	223931.71 (196388.58, 263117.43)	8.89 (6.68, 11.41)	-46136.09 (-109763.34, 9480.04)	42761.72 (-43808.08, 121177.06)
Glatiramer Acetate 20mg	224950.65 (193137.00, 272691.20)	8.99 (6.85, 11.42)	-45180.05 (-108191.80, 3871.31)	44705.25 (-37364.01, 110798.29)
Glatiramer Acetate 40mg	337478.58 (282825.09, 405125.50)	9.08 (6.80, 11.39)	-155811.32 (-212750.43, -99481.56)	-64977.69 (-128740.27, 1804.04)

Table 120 Costs, QALYs and Net Benefit for treatments in comparison to Natalizumab IV (publicly available list prices) for Scenario 9 (EID for natalizumab and natalizumab biosimilar)

Treatment	Total costs (95% CrI)	Total QALYs (95% CrI)	Net benefit at £20,000/QALY (95% CrI)	Net benefit at £30,000/QALY (95% CrI)
Natalizumab-IV	288775.97 (254232.66, 334444.50)	9.00 (6.66, 11.44)	-108751.14 (-165738.15, -60017.22)	-18738.72 (-98720.61, 47485.45)
Natalizumab-SC	288163.42 (256872.23, 337592.70)	9.04 (6.79, 11.57)	-107265.31 (-159581.61, -67743.20)	-16816.25 (-89709.75, 41981.19)
Natalizumab biosimilar-IV	282167.57 (250611.42, 323723.39)	9.01 (6.99, 11.64)	-102015.54 (-145845.30, -48413.03)	-11939.52 (-73777.97, 62118.38)
Natalizumab biosimilar-SC	307768.21 (274096.77, 361998.37)	8.92 (7.01, 11.45)	-129420.36 (-177875.09, -83836.00)	-40246.43 (-116490.99, 24062.04)
Fingolimod	277976.66 (237470.54, 323945.15)	9.12 (6.76, 11.61)	-95578.00 (-183903.15, -39142.56)	-4378.67 (-111136.75, 75668.47)
Alemtuzumab	256102.11 (224974.75, 310711.49)	8.83 (6.64, 11.45)	-79485.69 (-146505.10, -21454.56)	8822.53 (-76629.71, 85982.61)
Cladribine	270272.74 (240436.28, 311115.50)	8.92 (6.92, 11.41)	-91948.10 (-149066.77, -36691.54)	-2785.78 (-82275.46, 72631.01)

Treatment	Total costs (95% CrI)	Total QALYs (95% CrI)	Net benefit at £20,000/QALY (95% CrI)	Net benefit at £30,000/QALY (95% CrI)
Ponesimod	319109.33 (274917.17, 373221.66)	9.01 (6.80, 11.77)	-138875.93 (-200283.40, -86760.10)	-48759.23 (-125851.80, 28283.54)
Ofatumumab	333798.01 (284254.26, 403700.86)	9.09 (7.36, 11.45)	-151945.43 (-201801.51, -102751.24)	-61019.14 (-119155.09, 1136.43)
Ocrelizumab	226185.72 (202175.86, 265479.69)	8.94 (7.01, 11.53)	-47309.54 (-109563.12, 3805.09)	42128.55 (-39048.46, 115647.11)
Peginterferon-beta-1 SC 125µg	236380.81 (210401.37, 272389.62)	8.95 (6.77, 11.68)	-57332.52 (-123669.17, -618.69)	32191.62 (-59008.05, 114255.13)
Interferon-beta-1a SC 22µg	223719.61 (202341.21, 258351.54)	8.92 (6.63, 11.52)	-45346.13 (-115918.43, 5737.19)	43840.62 (-48486.22, 117107.61)
Interferon-beta-1a SC 44µg	226262.67 (198743.46, 266906.26)	8.85 (6.07, 11.34)	-49344.23 (-120602.66, 3302.12)	39115.00 (-54645.28, 112076.62)
Interferon-beta-1a IM 30µg	219677.47 (187880.13, 259462.40)	9.23 (7.13, 11.58)	-35125.32 (-94617.83, 9661.14)	57150.76 (-28067.36, 120526.75)
Interferon-beta-1b SC 250µg	218045.40 (190185.04, 266356.80)	8.88 (6.52, 11.60)	-40348.34 (-112001.33, 24636.95)	48500.19 (-41534.19, 139216.27)
Glatiramer Acetate 20mg	218456.91 (194647.46, 254425.19)	8.93 (6.77, 11.40)	-39863.02 (-99675.46, 12521.57)	49433.92 (-21836.22, 128421.85)
Glatiramer Acetate 40mg	288775.97 (254232.66, 334444.50)	9.00 (6.66, 11.44)	-108751.14 (-165738.15, -60017.22)	-18738.72 (-98720.61, 47485.45)

Table 121 Costs, QALYs and Net Benefit for treatments in comparison to Natalizumab IV (publicly available list prices) for Scenario 10 (OPERA edss 0-7 and Orme utilities edss 8-9 for RRMS & SPMS)

Treatment	Total costs (95% CrI)	Total QALYs (95% CrI)	Net benefit at £20,000/QALY (95% CrI)	Net benefit at £30,000/QALY (95% CrI)
Natalizumab-IV	336011.91 (284916.59, 400013.68)	10.37 (7.91, 11.98)	-128593.47 (-182663.77, -80465.69)	-24884.24 (-94909.66, 28804.86)
Natalizumab-SC	335777.83 (285679.76, 407757.26)	10.40 (8.39, 12.02)	-127843.06 (-194304.49, -84707.98)	-23875.67 (-104023.48, 20260.44)
Natalizumab biosimilar-IV	327490.71 (284435.59, 384059.22)	10.36 (8.45, 12.01)	-120326.52 (-176738.56, -81641.86)	-16744.43 (-84209.77, 28309.96)

Treatment	Total costs (95% CrI)	Total QALYs (95% CrI)	Net benefit at £20,000/QALY (95% CrI)	Net benefit at £30,000/QALY (95% CrI)
Natalizumab biosimilar-SC	314585.39 (277012.37, 372733.92)	10.26 (8.14, 12.17)	-109348.57 (-167697.26, -71853.12)	-6730.16 (-70227.81, 43536.68)
Fingolimod	284336.64 (248127.47, 326082.90)	10.49 (7.89, 12.10)	-74615.58 (-154659.92, -20290.26)	30244.95 (-79679.91, 95755.53)
Alemtuzumab	262827.40 (232532.60, 313558.51)	10.19 (8.10, 12.01)	-58954.93 (-117181.14, -11956.37)	42981.30 (-31905.50, 107795.71)
Cladribine	277068.27 (243247.72, 316716.08)	10.25 (8.13, 11.93)	-72086.47 (-131043.50, -34404.61)	30404.44 (-43613.69, 79034.25)
Ponesimod	325662.41 (277584.01, 387384.97)	10.36 (8.11, 12.38)	-118364.22 (-197397.73, -79609.09)	-14715.13 (-102425.74, 35366.04)
Ofatumumab	340721.47 (285874.31, 413237.22)	10.47 (8.89, 12.05)	-131409.15 (-194737.32, -88302.47)	-26752.99 (-89842.52, 14084.08)
Ocrelizumab	233155.05 (209551.42, 275050.64)	10.28 (8.14, 11.71)	-27556.91 (-88530.21, 12189.19)	75242.17 (-4610.56, 126901.12)
Peginterferon-beta-1 SC 125µg	243384.09 (218906.44, 278652.92)	10.30 (7.88, 12.22)	-37403.85 (-98457.17, 985.22)	65586.27 (-15400.78, 121554.92)
Interferon-beta-1a SC 22µg	230322.19 (207937.93, 262378.06)	10.26 (7.79, 11.95)	-25095.54 (-90387.00, 17941.07)	77517.78 (-5842.22, 135015.03)
Interferon-beta-1a SC 44µg	232766.70 (208082.19, 272659.85)	10.19 (7.66, 11.75)	-29063.73 (-98710.75, 12602.04)	72787.75 (-21696.08, 129941.17)
Interferon-beta-1a IM 30µg	226512.76 (195966.17, 265120.22)	10.57 (8.44, 12.17)	-15040.73 (-74927.78, 27932.92)	90695.29 (10963.72, 145169.80)
Interferon-beta-1b SC 250µg	224704.65 (198746.22, 270621.59)	10.22 (7.93, 11.82)	-20281.00 (-81552.06, 20923.24)	81930.83 (-4202.90, 139285.40)
Glatiramer Acetate 20mg	225479.38 (201711.77, 256044.60)	10.29 (8.33, 11.82)	-19701.68 (-84910.62, 21628.81)	83187.18 (7059.05, 140111.57)
Glatiramer Acetate 40mg	336011.91 (284916.59, 400013.68)	10.37 (7.91, 11.98)	-128593.47 (-182663.77, -80465.69)	-24884.24 (-94909.66, 28804.86)

Table 122 Costs, QALYs and Net Benefit for treatments in comparison to Natalizumab IV (publicly available list prices) for Scenario 11 (CLARITY edss 0-6 and Orme utilities edss 7-9 for RRMS & SPMS)

Treatment	Total costs (95% CrI)	Total QALYs (95% CrI)	Net benefit at £20,000/QALY (95% CrI)	Net benefit at £30,000/QALY (95% CrI)
Natalizumab-IV	336011.91 (284916.59, 400013.68)	10.51 (5.30, 17.19)	-125755.52 (-238065.96, -25084.26)	-20627.33 (-173472.14, 134965.25)
Natalizumab-SC	335777.83 (285679.76, 407757.26)	10.63 (5.92, 16.88)	-123188.47 (-218440.56, -10752.72)	-16893.79 (-148859.44, 142330.91)
Natalizumab biosimilar-IV	327490.71 (284435.59, 384059.22)	10.55 (6.13, 16.17)	-116531.66 (-216992.08, -5410.42)	-11052.14 (-150004.35, 165746.04)
Natalizumab biosimilar-SC	314585.39 (277012.37, 372733.92)	10.41 (5.98, 16.33)	-106330.31 (-196877.24, -5802.72)	-2202.78 (-133750.31, 156455.93)
Fingolimod	284336.64 (248127.47, 326082.90)	10.65 (5.96, 17.36)	-71353.12 (-164585.91, 44260.05)	35138.64 (-104914.48, 212967.27)
Alemtuzumab	262827.40 (232532.60, 313558.51)	10.33 (5.83, 16.60)	-56221.70 (-142557.55, 68622.49)	47081.16 (-82578.12, 223389.74)
Cladribine	277068.27 (243247.72, 316716.08)	10.37 (6.05, 16.11)	-69598.10 (-158638.05, 27173.47)	34136.99 (-97565.13, 182913.06)
Ponesimod	325662.41 (277584.01, 387384.97)	10.53 (6.07, 17.16)	-115137.75 (-217398.45, -15217.00)	-9875.43 (-150558.48, 166996.40)
Ofatumumab	340721.47 (285874.31, 413237.22)	10.63 (5.47, 17.13)	-128146.85 (-249347.91, -24608.59)	-21859.54 (-188776.32, 121466.91)
Ocrelizumab	233155.05 (209551.42, 275050.64)	10.50 (5.63, 16.45)	-23121.43 (-117230.35, 87146.17)	81895.38 (-54825.59, 252833.68)
Peginterferon-beta-1 SC 125µg	243384.09 (218906.44, 278652.92)	10.43 (5.59, 16.51)	-34758.62 (-134867.20, 82126.80)	69554.11 (-80177.51, 237598.37)
Interferon-beta-1a SC 22µg	230322.19 (207937.93, 262378.06)	10.48 (5.65, 17.26)	-20738.45 (-112683.87, 99361.25)	84053.42 (-54566.07, 266406.38)
Interferon-beta-1a SC 44µg	232766.70 (208082.19, 272659.85)	10.38 (5.57, 16.49)	-25208.35 (-124506.30, 77329.38)	78570.82 (-67984.83, 237858.22)
Interferon-beta-1a IM 30µg	226512.76 (195966.17, 265120.22)	10.75 (6.10, 16.18)	-11551.42 (-95184.48, 98273.33)	95929.25 (-29782.48, 256394.23)
Interferon-beta-1b SC 250µg	224704.65 (198746.22, 270621.59)	10.42 (5.94, 15.77)	-16240.35 (-109838.24, 100418.70)	87991.80 (-42986.40, 255524.39)

Treatment	Total costs (95% CrI)	Total QALYs (95% CrI)	Net benefit at £20,000/QALY (95% CrI)	Net benefit at £30,000/QALY (95% CrI)
Glatiramer Acetate 20mg	225479.38 (201711.77, 256044.60)	10.46 (5.56, 16.64)	-16349.09 (-115930.01, 99552.36)	88216.05 (-61005.19, 262819.42)
Glatiramer Acetate 40mg	336011.91 (284916.59, 400013.68)	10.51 (5.30, 17.19)	-125755.52 (-238065.96, -25084.26)	-20627.33 (-173472.14, 134965.25)

Table 123 Costs, QALYs and Net Benefit for treatments in comparison to Natalizumab IV (publicly available list prices) for Scenario 12 (TA127 for carer disutilities)

Treatment	Total costs (95% CrI)	Total QALYs (95% CrI)	Net benefit at £20,000/QALY (95% CrI)	Net benefit at £30,000/QALY (95% CrI)
Natalizumab-IV	336011.91 (284916.59, 400013.68)	10.74 (8.44, 13.07)	-121268.37 (-177924.70, -60364.89)	-13896.60 (-93802.30, 59362.51)
Natalizumab-SC	335777.83 (285679.76, 407757.26)	10.78 (8.50, 13.23)	-120176.94 (-178022.91, -67623.08)	-12376.49 (-73845.52, 56735.84)
Natalizumab biosimilar-IV	327490.71 (284435.59, 384059.22)	10.74 (8.64, 13.27)	-112617.60 (-165742.16, -56930.78)	-5181.04 (-65418.15, 69152.21)
Natalizumab biosimilar-SC	314585.39 (277012.37, 372733.92)	10.66 (8.69, 13.16)	-101456.36 (-149136.69, -49467.20)	5108.15 (-66346.85, 77255.02)
Fingolimod	284336.64 (248127.47, 326082.90)	10.84 (8.33, 13.40)	-67457.79 (-151372.11, -12169.48)	40981.64 (-59205.89, 115517.79)
Alemtuzumab	262827.40 (232532.60, 313558.51)	10.58 (8.11, 13.18)	-51269.28 (-115060.73, 4152.27)	54509.78 (-30625.90, 130237.23)
Cladribine	277068.27 (243247.72, 316716.08)	10.68 (8.53, 13.31)	-63538.40 (-117677.97, -11393.04)	43226.54 (-33739.13, 115906.57)
Ponesimod	325662.41 (277584.01, 387384.97)	10.74 (8.31, 13.33)	-110901.35 (-173126.36, -55096.60)	-3520.82 (-82211.04, 71810.05)
Ofatumumab	340721.47 (285874.31, 413237.22)	10.84 (9.08, 13.25)	-123979.71 (-183668.80, -68150.79)	-15608.84 (-81973.28, 50268.92)
Ocrelizumab	233155.05 (209551.42, 275050.64)	10.69 (8.66, 13.18)	-19301.82 (-78564.46, 27095.07)	87624.79 (13041.17, 153472.18)
Peginterferon-beta-1 SC 125µg	243384.09 (218906.44, 278652.92)	10.69 (8.47, 13.39)	-29495.21 (-92654.26, 20198.89)	77449.22 (-14540.01, 149176.79)

Treatment	Total costs (95% CrI)	Total QALYs (95% CrI)	Net benefit at £20,000/QALY (95% CrI)	Net benefit at £30,000/QALY (95% CrI)
Interferon-beta-1a SC 22µg	230322.19 (207937.93, 262378.06)	10.66 (8.18, 13.33)	-17207.81 (-86365.33, 32568.17)	89349.39 (-3470.97, 164304.41)
Interferon-beta-1a SC 44µg	232766.70 (208082.19, 272659.85)	10.58 (7.54, 12.99)	-21205.82 (-90605.56, 30115.41)	84574.62 (-11812.39, 155468.11)
Interferon-beta-1a IM 30µg	226512.76 (195966.17, 265120.22)	10.93 (8.86, 13.24)	-7841.60 (-63494.34, 39024.86)	101493.98 (19102.14, 165066.99)
Interferon-beta-1b SC 250µg	224704.65 (198746.22, 270621.59)	10.65 (8.25, 13.30)	-11793.42 (-82809.70, 48615.70)	94662.20 (3631.20, 180069.65)
Glatiramer Acetate 20mg	225479.38 (201711.77, 256044.60)	10.68 (8.53, 13.18)	-11817.72 (-68863.95, 36797.14)	95013.12 (22370.85, 168403.49)
Glatiramer Acetate 40mg	336011.91 (284916.59, 400013.68)	10.74 (8.44, 13.07)	-121268.37 (-177924.70, -60364.89)	-13896.60 (-93802.30, 59362.51)

Table 124 Costs, QALYs and Net Benefit for treatments in comparison to Natalizumab IV (publicly available list prices) for Scenario 13 (mortality by severity edss<4 Jick et al and edss≥4 Harding et al)

Treatment	Total costs (95% CrI)	Total QALYs (95% CrI)	Net benefit at £20,000/QALY (95% CrI)	Net benefit at £30,000/QALY (95% CrI)
Natalizumab-IV	327638.18 (277665.06, 392895.16)	8.84 (6.93, 10.98)	-150755.96 (-210012.19, -101609.82)	-62314.84 (-131818.76, -5209.01)
Natalizumab-SC	323453.46 (278850.07, 385756.58)	8.78 (6.77, 10.57)	-147917.56 (-201803.87, -90083.99)	-60149.61 (-126344.81, 8209.33)
Natalizumab biosimilar-IV	316688.26 (273871.65, 382029.76)	8.84 (6.92, 11.29)	-139831.85 (-186255.10, -86442.86)	-51403.65 (-111516.56, 12140.50)
Natalizumab biosimilar-SC	304742.40 (270121.58, 341351.48)	8.69 (6.96, 10.93)	-130871.13 (-178458.92, -75687.90)	-43935.50 (-109070.52, 19423.08)
Fingolimod	275262.80 (252695.85, 308908.12)	8.86 (6.47, 10.90)	-98144.34 (-163105.59, -48318.82)	-9585.12 (-87803.35, 59643.23)
Alemtuzumab	252989.49 (227342.52, 292066.69)	8.57 (6.63, 10.53)	-81598.08 (-151113.04, -30766.50)	4097.63 (-81172.87, 71933.97)
Cladribine	266100.33 (233785.36, 311502.74)	8.61 (6.34, 10.53)	-93993.91 (-154847.27, -46523.87)	-7940.70 (-83554.72, 56574.78)

Treatment	Total costs (95% CrI)	Total QALYs (95% CrI)	Net benefit at £20,000/QALY (95% CrI)	Net benefit at £30,000/QALY (95% CrI)
Ponesimod	315108.14 (273357.74, 370803.20)	8.78 (6.93, 10.72)	-139413.88 (-179255.99, -83678.83)	-51566.75 (-98472.99, 13700.74)
Ofatumumab	327289.95 (276339.26, 394937.54)	8.84 (6.75, 10.69)	-150433.19 (-212800.84, -92596.23)	-62004.81 (-135923.16, 1934.78)
Ocrelizumab	222994.03 (193671.78, 258197.68)	8.76 (6.85, 10.66)	-47748.08 (-105956.93, -6118.09)	39874.90 (-32846.89, 94636.00)
Peginterferon-beta-1 SC 125µg	231743.81 (206494.86, 271328.93)	8.56 (6.08, 10.73)	-60613.91 (-128689.32, -8420.97)	24951.04 (-64686.50, 96711.58)
Interferon-beta-1a SC 22µg	221778.05 (198404.87, 253078.21)	8.69 (6.43, 11.06)	-47972.03 (-108429.81, -1815.87)	38930.97 (-39701.53, 107028.78)
Interferon-beta-1a SC 44µg	223822.67 (199610.35, 259892.01)	8.69 (6.32, 10.88)	-50019.27 (-113649.22, -7098.52)	36882.44 (-41736.12, 100125.47)
Interferon-beta-1a IM 30µg	215589.88 (189812.25, 252265.68)	8.87 (6.49, 10.87)	-38262.04 (-107486.47, 12472.45)	50401.88 (-37313.15, 118317.33)
Interferon-beta-1b SC 250µg	214092.35 (192340.89, 247611.11)	8.58 (6.25, 10.75)	-42434.04 (-101493.26, 6823.30)	43395.11 (-29216.71, 113335.71)
Glatiramer Acetate 20mg	213868.87 (186247.42, 244877.20)	8.64 (6.47, 10.90)	-40984.41 (-92406.66, 12066.06)	45457.82 (-23252.58, 117890.74)
Glatiramer Acetate 40mg	327638.18 (277665.06, 392895.16)	8.84 (6.93, 10.98)	-150755.96 (-210012.19, -101609.82)	-62314.84 (-131818.76, -5209.01)

Table 125 Costs, QALYs and Net Benefit for treatments in comparison to Natalizumab IV (publicly available list prices) for Scenario 14 (NMA where CPD3 is used for studies with missing CDP6)

Treatment	Total costs (95% CrI)	Total QALYs (95% CrI)	Net benefit at £20,000/QALY (95% CrI)	Net benefit at £30,000/QALY (95% CrI)
Natalizumab-IV	336236.94 (282761.41, 410288.88)	9.04 (7.05, 11.68)	-155474.27 (-205127.79, -99284.69)	-65092.93 (-132474.85, 13912.64)
Natalizumab-SC	337672.05 (289833.98, 404807.78)	9.00 (6.96, 11.44)	-157699.96 (-204961.91, -108003.40)	-67713.91 (-131024.51, -2027.14)
Natalizumab biosimilar-IV	327461.53 (279504.28, 394648.37)	9.10 (7.06, 11.76)	-145363.91 (-199514.10, -84863.99)	-54315.10 (-125534.22, 19599.68)

Treatment	Total costs (95% CrI)	Total QALYs (95% CrI)	Net benefit at £20,000/QALY (95% CrI)	Net benefit at £30,000/QALY (95% CrI)
Natalizumab biosimilar-SC	314583.93 (275173.69, 376522.93)	9.02 (6.82, 11.79)	-134177.24 (-186490.54, -81386.85)	-43973.90 (-112931.72, 26212.54)
Fingolimod	284745.73 (255177.65, 334009.33)	9.10 (6.83, 11.50)	-102774.46 (-175712.75, -51922.14)	-11788.83 (-100125.71, 59161.32)
Alemtuzumab	261523.68 (230405.95, 301352.40)	8.95 (6.90, 11.32)	-82549.76 (-144866.91, -27819.23)	6937.20 (-70449.90, 83185.84)
Cladribine	276341.26 (244931.33, 315399.61)	8.89 (6.42, 11.61)	-98445.85 (-153084.15, -45014.43)	-9498.15 (-90056.32, 69021.63)
Ponesimod	326145.69 (278861.93, 389731.89)	9.07 (7.11, 11.47)	-144727.04 (-200412.73, -93130.42)	-54017.71 (-122607.86, 4515.70)
Ofatumumab	339989.98 (285579.52, 417233.80)	9.12 (6.96, 11.57)	-157503.67 (-209680.27, -94001.15)	-66260.51 (-125705.62, 10218.77)
Ocrelizumab	231414.38 (204849.57, 271271.18)	9.08 (6.89, 11.60)	-49824.84 (-110287.22, 1351.00)	40969.92 (-38308.17, 114832.44)
Peginterferon-beta-1 SC 125µg	242169.39 (218724.10, 284055.34)	8.98 (6.70, 11.61)	-62503.85 (-122684.96, -16852.74)	27328.93 (-54248.37, 96817.32)
Interferon-beta-1a SC 22µg	231171.98 (207517.99, 263284.98)	8.95 (6.51, 11.67)	-52097.26 (-112829.57, -3857.71)	37440.10 (-43554.86, 106152.13)
Interferon-beta-1a SC 44µg	234093.27 (208446.40, 274763.54)	8.78 (6.36, 11.16)	-58456.74 (-135210.73, -11450.63)	29361.53 (-65327.05, 94996.25)
Interferon-beta-1a IM 30µg	227961.39 (201601.27, 274337.76)	8.76 (6.52, 11.25)	-52798.58 (-119844.28, -573.03)	34782.82 (-54740.62, 108214.58)
Interferon-beta-1b SC 250µg	224567.98 (193043.29, 272780.41)	8.90 (6.34, 11.56)	-46660.46 (-117570.63, 2193.62)	42293.29 (-50196.27, 116149.16)
Glatiramer Acetate 20mg	223736.05 (202262.02, 262873.62)	8.91 (6.48, 11.25)	-45444.36 (-113664.60, 5442.07)	43701.48 (-47752.69, 117224.48)
Glatiramer Acetate 40mg	336236.94 (282761.41, 410288.88)	9.04 (7.05, 11.68)	-155474.27 (-205127.79, -99284.69)	-65092.93 (-132474.85, 13912.64)

NICE National Institute for Health and Care Excellence

Multiple Technology Appraisal

Natalizumab and Tyruko (natalizumab biosimilar) for treating highly active relapsing-remitting multiple sclerosis after at least one disease modifying therapy [ID6369]

External Assessment Group Report consultation response form

As a stakeholder you have been invited to comment on the External Assessment Group (EAG) Report for this appraisal.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

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Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

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The deadline for comments is **5pm** on **08 January 2025**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).Thank you for your time.

About you

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Biogen Idec Ltd
Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	Biogen Idec Ltd are the manufacturer of Natalizumab (Tysabri) IV & SC, hereafter defined as natalizumab-TYS
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry	N/A

NICE National Institute for Health and Care Excellence

Comments on the External Assessment Report

Page No. (Paragraph)	Related Text	Company Comment	Resolution
Full report	Not applicable	Biogen would like to thank the Expert Advisory Group (EAG) for their thorough and detailed assessment of the decision problem. Below is a summary of our feedback on the draft report, including requests for further detail, particularly regarding the MS Registry analyses and outputs from the economic model, and suggestions for updates to address aspects of the value of natalizumab-TYS that have not been fully documented or were excluded from the base case of the economic evaluation. To fully and robustly reflect the value of natalizumab-TYS, we believe that the updated base case and key sensitivity analyses should include: 1. **Cost savings associated with natalizumab SC:** The base case should reflect the Biogen-funded natalizumab-TYS SC home injection service,[1] and the cost, time efficiency, reduced patient burden and patient preference improvements provided by natalizumab-TYS SC compared with IV (see pages 5–7 for further details). 2. **Biogen-funded JCV testing:** The base case should be updated to reflect that JCV testing is nationally available for natalizumab-TYS, funded by Biogen. and to remove	To update the report, base case and key sensitivity analyses as described

Page No. (Paragraph)	Related Text	Company Comment	Resolution
		costs associated with JCV testing from the natalizumab-TYS (IV & SC) (see pages 7–9 for further details).[2] 3. **Extended interval dosing (EID) for natalizumab:** EID, administering natalizumab-TYS IV or SC Q6W or Q8W instead of SID Q4W should be included as a key sensitivity analysis. EID is used in clinical practice for some UK patients,[3,4] and provides other benefits for patients and the NHS (see pages 9–10 for further details). 4. **Tender pricing:** Drug acquisition costs in the base case economic analysis should be updated to reflect those paid by the NHS in routine practice, namely those associated with procurement via national tender processes (see pages 10–11 for further details). 5. **Comparators:** Based on the NHS England DMT algorithm presented in the CS and the EAG report, the appropriate comparators for the base case for the economic analysis are ofatumumab, ponesimod and cladribine (see pages 11–13 for further details). 6. **Remaining factual accuracies in the EAG report and the R-based model:** these are detailed in the table below	

Page No. (Paragraph)	Related Text	Company Comment	Resolution
General comments and preferred base case/key sensitivity analyses			
Full report	Not applicable	The external validity of the model has been challenging to assess, as many key clinical outputs are not presented within the report. While we ran the model for 100 iterations using the code shared (without making any edits), our observations raised validity concerns regarding the age at death, the duration of time spent in EDSS health states, and the duration on treatment at each line of therapy. These outputs appear inconsistent with expectations – as described in detail below. However, it would be more informative to have these outputs directly from the EAG's original analysis to facilitate a thorough assessment. This would enhance transparency and provide a stronger basis for evaluating the model's validity.	Provide key clinical outcomes predicted by the model for transparency and such that these outcomes can be externally validated, including (non-exhaustive) the age of death, duration of time spent in EDSS health states, and the duration on treatment at each line of therapy.
Subcutaneous natalizumab-TYS – value and administration costs			
Page 128 (3)	*"The manufacturers anticipate cost savings associated with the administration and monitoring of Natalizumab*	This statement is inconsistent with published evidence, which demonstrates clear differences in the costs and benefits accrued to the healthcare system between natalizumab SC and IV administration. Silingardi et al. (2023), as described on page 55 of the CS, report a time and motion study conducted in Salford, an outpatient department of the tertiary neurology service in Greater Manchester that provides DMT treatment for patients with MS.[5] The study found that natalizumab SC significantly reduced	The base case should remove the administration costs associated with natalizumab-TYS (SC) to reflect the demonstrated cost savings associated with natalizumab SC compared to natalizumab IV. The report should acknowledge that these benefits

Page No. (Paragraph)	Related Text	Company Comment	Resolution
	Sub Cutaneous (SC) in comparison to the intravenous (IV) deliver. However, our clinical advisors explained that in practice patients do not see differences between SC and IV in intensity of resource use."	workload and increased available staff and chair time, with total time savings of 1 hour and 32 minutes per patient compared to natalizumab IV administration. These findings are corroborated by cost-analyses conducted in Spain and Italy, which showed that cost savings associated with natalizumab SC were largely driven by reduced administration costs and increased patient and caregiver productivity, as described on pages 51–52 of the CS.[6,7] Furthermore, this statement does not consider the Biogen-funded natalizumab SC home injection service. This service allows patients to receive their natalizumab SC injections at home, thereby reducing the need for hospital visits. The service includes the delivery of the medicine directly to patients' homes and administration by a Biogen-funded homecare nurse, providing additional cost and potential VAT savings to the NHS.[1] Patient preferences further highlight the value of natalizumab SC. In the NOVA (Part 2) study, the majority of participants on Q6W dosing preferred SC administration over IV, with 82.9% citing "requires less time in clinic" as a key reason for their preference.[8] Similarly, the TONIC study highlighted that all but one patient who switched from IV to SC expressed either a "fairly strong" or "very strong" preference for natalizumab SC compared to natalizumab IV driven by time savings.[9] These findings are corroborated by the published SISTER (Subcutaneous: Non-Interventional Study for Tysabri Patient Preference – Experience from Real World) study	extend beyond those captured by the economic evaluation.

Page No. (Paragraph)	Related Text	Company Comment	Resolution
		indicated a strong trend toward patient preference for the SC route over the IV route.[10] As well as reducing burden on NHS by freeing up nursing and infusion chair time, natalizumab SC has important benefits in reducing the burden on patients through enabling care closer to home. This minimises the travel and treatment time for patients, helping to address health inequalities and reduce associated patient costs, such as transportation, childcare, and lost productivity due to time away from work. The demonstrated differences in costs, time efficiency, patient burden, and overall preference underline the importance of recognising the broader benefits of natalizumab SC over IV administration. These factors are supported by robust evidence and should be reflected in the economic evaluation.	
JCV testing			
Page 22 (4)	*"The cost of John Cunningham human polyomavirus (JCV) testing was included for*	At multiple points throughout the report it is stated that JCV testing for natalizumab-TYS and biosimilar is not widely available. This is factually inaccurate for natalizumab-TYS, for which JCV testing is available and funded in the UK for all patients being considered for treatment with natalizumab-TYS.[2] Biogen funded [redacted] Stratify JCV tests between Jan 2024 and Nov 2024 for patients being considered for natalizumab-TYS.	To update the report to reflect that JCV testing is nationally available for natalizumab-TYS, funded by Biogen. and to remove costs associated with JCV testing from the natalizumab-TYS (IV & SC)

Page No. (Paragraph)	Related Text	Company Comment	Resolution
	both natalizumab and natalizumab biosimilar as clinical advice was that the manufacturer scheme of paying for JCV testing is not widely available"		arms in the base case of the economic evaluation.
Page 118 (2)	*"However, our clinical advice was that this scheme is not widely implemented so the cost of JCV testing was included for natalizumab"*	As above	As above
Page 118 (2)	*"Progressive Multifocal Leucoencephalopathy (PML) is an important side effect of*	PML also occurs with other MS treatments, as stated in the SmPCs for ocrelizumab, ofatumumab, cladribine, fingolimod, ponesimod and alemtuzumab.	Update the report to provide a more balanced summary of the risk of PML across the relevant therapies within the decision problem.

Page No. (Paragraph)	Related Text	Company Comment	Resolution
	some MS drugs, particularly natalizumab and its biosimilar"		
Lack of consideration of Extended Interval Dosing (EID)			
Page 52 (5)	*"Interventions: We restricted inclusion to studies that evaluated the interventions of interest at modes of administration and doses licensed for use in UK unless they were required to create a connected network."*	EID, administering natalizumab-TYS IV or SC Q6W or Q8W instead of SID Q4W is used in clinical practice for some patients (UK clinical opinion).[3,4] Additionally, EID (Q6W) is outlined in the natalizumab-TYS SmPC.[11,12] As described on p15 of the CS, " In clinical practice [redacted][13] doses of natalizumab-TYS are administered per patient/year". Rabea et al. (2023) assessed the difference in the efficacy and safety of the EID regimen compared with the SID of natalizumab for patients with MS based on a meta-analysis of data identified in an SLR; the study found that EID did not diminish the effectiveness of natalizumab therapy, with a lower risk of clinical relapse and developing newly enlarging T2 hyperintense lesions.[14] These data align with the results from the natalizumab observational program presented at the European Academy of Neurology in 2024; efficacy was similar in patients switching from IV to SC formulation, regardless of SID or EID dosing.[15] Additional benefits of EID are:	Biogen requests that EID is given due consideration in the EAG report, and that the cost savings associated with EID for natalizumab-EID are included in key sensitivity analyses within the economic assessment.

Page No. (Paragraph)	Related Text	Company Comment	Resolution
		1. Cost savings to the NHS (drug costs and HCP time for drug administration). 2. A reduction in natalizumab-TYS exposure during pregnancy. 3. A reduction in the risk of PML. 4. A reduction in travel and in-clinic time for some patients and carers for drug administration. There is little reference to EID throughout the EAG report.	
Page 127 (3)	*"The number of annual doses for Natalizumab are in line with those reported in the Biogen submission"*	This is factually inaccurate as it does not take into account the EID dosing schedule for which evidence was presented in the CS.	To include EID as a key sensitivity analyses and update the report as needed.
Drug acquisition costs based on real-world tender pricing			
Table 20, page 124	*"The annual drug acquisition costs are in line with the costs of Natalizumab, Natalizumab bio similar,*	Biogen is concerned that the drug acquisition cost for natalizumab-TYS is inflated beyond that paid for by the NHS. Natalizumab-TYS is available at a confidential discount provided via national tender agreements that are applicable across all of England. The drug acquisition costs for natalizumab-TYS also do	Drug acquisition costs in the base case economic analysis should be updated to reflect those paid by the NHS in routine practice.

Page No. (Paragraph)	Related Text	Company Comment	Resolution
	Ofatumumab and Ocrelizumab reported in the Sandoz submission." *"The number of annual doses for Natalizumab are in line with those reported in the Biogen submission."*	not reflect the use in UK clinical practice of EID, as described in more detail above.	
Comparators			

Page 21, 40, 112, 120	*Page 40: "The comparator for this appraisal is standard care without natalizumab or natalizumab biosimilar. This includes the following interventions:* *• Glatiramer acetate* *• Interferon beta 1a* *• Interferon beta 1b* *• Alemtuzumab* *• Cladribine tablets* *• Fingolimod* *• Ocrelizumab.* *The NICE scope suggested that this should only be if alemtuzumab is contraindicated. However, our clinical advisors*	Biogen is concerned that the comparators included in the appraisal are broader than – and therefore not fully reflective of – those therapies used in UK clinical practice. The NHS England treatment algorithm for MS DMTs (shown in Figure 1, page 34 in the EAG report) outlines the relevant treatment options for patients who have received a full and adequate course of at least 1 DMT. These options do not include glatiramer acetate, interferon beta 1a or interferon beta 1b, and these therapies are therefore not considered appropriate comparators for this appraisal. Although these low/moderate efficacy DMTs have been used historically as treatment options for patients with highly active relapsing–remitting multiple sclerosis they are now rarely used in clinical practice due to the current availability of high-efficacy DMTs (UK clinical opinion)[3,4,16] Furthermore none of the recent appraisals in MS included IFNs and GA as comparators in this subgroup (see final scopes) e.g. TA 533, TA 699, TA767. Moreover, as outlined on page 8 of the CS for natalizumab-TYS, fingolimod, alemtuzumab and autologous haematopoietic stem cell transplantation are not considered relevant comparators to natalizumab-TYS. [redacted][17]	Removal of inappropriate comparators from the decision problem (IFNs and GA). Base case economic analysis to focus on ocrelizumab, ofatumumab, ponesimod and cladribine.

	suggested that this is not reflective of this drug is used in clinical practice and so we will not apply this restriction for our appraisal. *• Ofatumumab* *• Ponesimod* *• Autologous haematopoietic stem cell transplantation"*	Fingolimod use is expected to decline further in the future due to the requirement for CV and skin lesion monitoring (UK clinical opinion).[3,4,16] Autologous haematopoietic stem cell transplantation is used as a last-line therapy when high-efficacy DMT options have been exhausted (UK clinical opinion).[3,4,16] Autologous haematopoietic stem cell transplantation is only available in a small number of NHS centres and very few people with multiple sclerosis are accepted for treatment.[18,19] Alemtuzumab is also considered as last-line therapy for the majority of patients when other DMT options have been exhausted (UK clinical opinion).[4,16] Alemtuzumab is associated with serious adverse events, including thyroid disorders, immune thrombocytopenic purpura and kidney disease.[20]	
Definition of the target population			
Page 31 (2)	*"There is a lack of consensus regarding the definitions for the varying subtypes of disease, with different*	Biogen agree that there is a lack of consensus regarding subgroup definitions, and would welcome NICE aligning these definitions. Inconsistency in definitions across technology appraisals brings challenges regarding selecting appropriate evidence on which to base robust decision making.	NICE to confirm definition of appropriate subgroups within RRMS, and then apply to this technology appraisals as appropriate.

	appraisals and studies using slightly different definitions. "		
Page 31, Table 2	*"No consensus definition; previous appraisals for NICE have used different definitions. We will use the following broad definition for this appraisal to encompass the variety of different definitions used in existing trials: Unchanged or increased clinical or radiological evidence of disease activity despite treatment with at least one Disease*	Regarding the proposed definition of the target population, Biogen suggest that this should specify at least 12 months of prior DMT to rule out tolerance issues. It may also be helpful, given the differences in definitions in previous appraisals, to include those definitions in this report, for clarity and comparison. Finally, it would be helpful to include that rapidly evolving severe (RES) RRMS comprises a subgroup of patients within highly active RRMS. For example, patients with 2 relapse events within a 12-month period would be considered to meet the criteria for both RES and highly active RRMS.	To update the report as suggested

	Modifying Therapy (DMT)"		
Identification of relevant evidence for, and conduct of, network meta-analysis to support decision making			
Page 26 (2)	*"There is no direct evidence on the effectiveness of natalizumab or its biosimilar in patients with highly active disease"*	This statement is only correct based on the restricted criteria for the systematic literature review conducted by the EAG. The CS for natalizumab-TYS includes extensive real-world evidence for the patient population specified in the decision problem, mostly notably from the TOP study. TOP is the largest real-world study of natalizumab-TYS 300 mg IV in patients with RRMS and provides more than 15 years' follow-up for patients which include those with "highly active disease despite a full and adequate course of treatment with ≥1 DMT". Data from TOP was the pivotal efficacy evidence for the extension of the licensed indication for natalizumab-TYS.[21]	Biogen would request that the real-world evidence presented in the CS is given due weight in the decision-making process for this appraisal, consistent with NICE's own framework on incorporating this evidence class in technology appraisals.
Page 55 (3) Page 79 (3)	*"We therefore expanded our inclusion criteria to include studies that compared ofatumumab to other interventions not specified in our original inclusion criteria. This lead to the*	It is unclear why studies evaluating teriflunomide vs ofatumumab have been included yet studies evaluating teriflunomide vs. placebo have not been utilised to create a fully connected network. There is also a minor typographical error ("lead" should be "led").	Explore including the teriflunomide studies TOWER[22] and TESMO[23] to enable the construction of a fully connected network for NMA. Amend the typographical error.

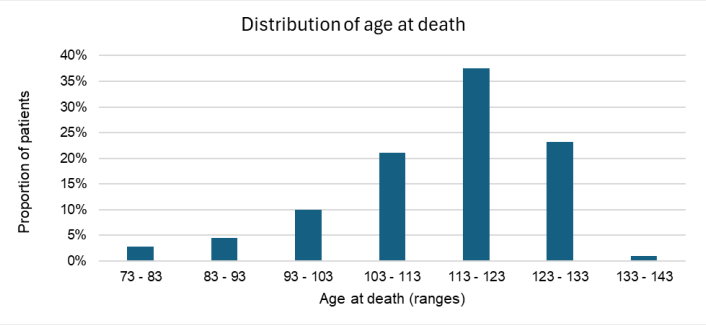
	inclusion of an additional 2 studies: ASCLEOPIO I and II[68] that compared ofatumumab to teriflunomide. To create a connected network, we also included the OPTIMUM trial[70] that compared teriflunomide with ponesimod. These three studies are included in our total number of 42 included studies" *"for both outcomes, teriflunomide, ponesimod and ofatumumab did not connect to the network. We were therefore*		

	unable to include these interventions in the NMA"		
Table 8, page 77	*Outcomes based on the INCOMIN trial*	No commentary, or sensitivity analyses, is provided around the Interferon beta 1b IM 250 study. In general, there is usually high correlation between CDP3 and CDP6 endpoints. However, CDP3 and CDP6 MTC outputs for IFNB-1b are inconsistent (INCOMIN is the only study informing CDP6 for IFNB-1b). The INCOMIN trial, investigating IFNB-1b compared to IFNB-1a, should be excluded from the base case analysis for CDP6 as it is widely considered an outlier by clinical experts. This approach is consistent with the technology appraisals for ocrelizumab (TA533) and ofatumumab (TA699).[24,25]	To remove the INCOMIN study from the analysis
Page 79 (2)	*"Studies reported disease progression at between 6 and 24 months follow-up, with a median of 24 months follow-up. "*	It is unclear if all studies have been included regardless of study duration or if some restriction has been applied. Biogen would recommend the latter. It is also concerning that study durations of 6 months were included, as disability progression requires confirmation 3 or 6 months post-initial assessment and this is unlikely to have been possible for studies of 6 months' duration or less.	To clarify the criteria for selecting included studies and conduct sensitivity analyses restricting study durations e.g. 24 months only.
Page 23 (3), Page 67 (1)	*"All studies were considered to be sufficiently similar for*	Biogen appreciate the difficulty in aligning patient populations and study designs across studies of RRMS which has been a historical issue in previous and ongoing appraisals. The studies	Provide more clarity with regards to the impact of key differences across the studies included within

	inclusion in the NMAs."	identified by the EAG and incorporated into the NMA include a range of types of MS, different diagnostic criteria of MS, ages of patients, and other factors that are prognostic of progression of disease. Within the studies identified – which themselves include a population broader than that specified in the decision problem – there is sufficient heterogeneity to create uncertainty in the comparative clinical efficacy across the therapies relevant to this appraisal.	the NMA on the results. Additionally, add any supporting evidence or validation conducted supporting the assumption that the studies are sufficiently similar for inclusion in the NMA.
Page 52 (6)	*"Outcomes: Due to time and resource constraints, we restricted inclusion to studies that reported on at least one of the following outcomes:*	We note that the list of relevant outcomes does not include disease *regression or improvement*. In a recent meta-analysis published by Chappell et al – and included in the CS - there were higher rates of confirmed disability improvement (CDI) for patients receiving natalizumab compared with platform DMT at 24 months and this was significant for 3-month confirmation ($p < 0.0001$).[26] Real-world data from MSBase also highlight improvements in disease outcomes for patients treated with natalizumab.[27,28] Spelman *et al* demonstrated that switching to natalizumab after an inadequate response to first-line therapies (interferon-based therapies, glatiramer acetate, dimethyl fumarate, and teriflunomide) was associated with a significant increase in CDI at 6 months (HR = 1.28; 95% CI 1.01–1.62; $p = 0.040$) compared with switching to fingolimod.[27] Similarly, a Cox regression model based on MSBase data by Butzkueven *et al* showed that patients who initiated natalizumab as first-line therapy had a more favourable time-to-first clinical disease improvement than patients	To clarify why disease regression was not included in the outcomes

		who initiated interferon-based therapies, glatiramer acetate, dimethyl fumarate, or teriflunomide.[28] Together, these data highlight that importance of disease regression or improvement as a relevant clinical outcome that should be included in the EAG's analysis.	
Figure 5, Page 73	*"Figure 5 Forest plot of hazard ratios (HR) and 95% credible intervals for time to CDP3 (fixed effects NMA; RRMS population)"*	The x-axis states "Rate Ratio (RR)" – this should be "Hazard Ratio (HR)". Additionally, for clarity it should be added that the hazard ratios are relative to placebo. There is no explanation provided with regards to the wide confidence intervals for peginterferon beta 1a SC125.	Update x-axis title and add clarification with regards to the reference treatment. Provide narrative explaining the cause of the wide confidence intervals for peginterferon beta 1a SC125.
Figure 6, Page 74	*"Figure 6 Forest plot of hazard ratios (HR) and 95% credible intervals from fixed effects NMA for time to CDP6 (fixed effects NMA; RRMS population)"*	It is unclear why direct evidence is only depicted for natalizumab IV300, fingolimod O0.5, and cladribine O3.5 when most studies are placebo controlled e.g., peginterferon beta 1a SC125 and interferon betas.	Update the figure to include other direct evidence sources or provide narrative explaining the exclusion of other placebo-controlled studies.
Pages 74–77	Text related to NMAs and related Forrest plots	It would improve clarity and readability to keep the relevant Forrest plots next to the text where the results are discussed	To re-flow the figures so that they are adjacent to the relevant text

Insufficient information available on the modelling approach			
Section 6	There is insufficient information presented on the modelling assumptions, inputs, and outputs.	There is insufficient information presented on the modelling assumptions, inputs, and outputs. Some examples are provided below. It is the Company's view that all inputs used in the modelling should be presented in the report. This is important for transparency and allows the validity of assumptions and inputs to be assessed. Furthermore, whilst the London Ontario MS dataset is discussed, it is unclear whether these data inform the base case or any sensitivity analyses. Furthermore, the following outputs should be presented from the economic model such that the external validity of the results can be assessed: • Duration spent in EDSS health states. Based on the R code provided by the EAG, we ran the model for 100 patients across the 17 therapies without making any changes to the shared code. The resulting durations of time spent in EDSS health states appear longer than anticipated for patients with RRMS. • Duration on treatment at each line of therapy. Based on the R code provided by the EAG, we ran the model for 100 patients across the 17 therapies without making any changes to the shared code. The resulting durations on treatment appear longer than anticipated for patients with RRMS. • Undiscounted life years	All assumptions used in the modelling should be stated and justified in the EAG report. All inputs used in the modelling should be presented in the EAG report. Relevant clinical outputs should be presented in the EAG report such that the validity of the model can be assessed.

		• Undiscounted QALYs	
Section 6	As described in the row above, there is insufficient information presented on the validity of outputs from the model.	Based on the R code provided by the EAG, we ran the model for 100 patients across the 17 therapies without making any changes to the shared code. The resulting age at death appears significantly higher than expected for patients with RRMS and even exceeds the life expectancy of the UK age- and gender-matched general population (Figure 1). While this observation is derived from our model run, it underscores the importance of presenting model outputs in a way that allows for external validation. Currently, there is insufficient information to assess whether the age at death generated by the EAG model aligns with external data and can be considered valid. **Figure 1: Distribution of age at death across 100 simulations for 17 therapies** 	Relevant clinical outputs should be presented in the EAG report such that the validity of the model can be assessed for the base case and key sensitivity analyses.

Page 134 (2)	*"The standardized mortality ratio in base case analysis was reported in a case control study of (N=1822) MS patients follow-up up till death (Jick 2014).137 An all-cause mortality Hazard ratio 1.68 (95% CI: 1.38-2.05) compared to the general population was estimated using a proportional hazards cox model"*	Following ongoing discussions as part of the cladribine NICE submission (GID-TA11293), the preference from the EAG in the ongoing appraisal is to apply EDSS-specific SMRs in the base case.[29] Additionally and in relation to the row above, limited information is provided on the clinical outcomes predicted by the model in the sensitivity analysis assuming EDSS-specific SMRs.	The SMR applied to the health states in the base case should align with the latest clinical, EAG, and Committee discussions from relevant NICE appraisals. If an alternative approach is taken, the justification and impact of this should be presented. As above, relevant clinical outputs should be presented in the EAG report such that the validity of the model can be assessed for the base case and key sensitivity analyses.
Page 25 (4) and figure 25, Page 142	*"Validation of EDSS severity over time found less severe trend that was*	In Figure 25 a graph is presented titled "*Validation through comparison of EDSS severity over time from economic model (red line with 95% CrI) and predictions from Palace 2014 (purple and green)*". However, it is unclear whether the red line from the EAG	Provide clarity on the validation of EDSS severity conducted and the graph presented in Figure 25.

	explained by the comparator model mixing RRMS and SPMS patients and not using the latest DMT sequences."	economic model reflects the natalizumab arm or, in line with the PALACE data, the interferon beta and glatiramer acetate arms. Note: the code used to re-create this graph was unavailable within the R code shared by the EAG.	
Page 121 (5)	*Baseline rates of discontinuation due to AEs provided a proxy to waning as in previous appraisals, and were assumed to follow the AFFIRM study for natalizumab and ANTELOPE study for natalizumab biosimilar. For comparators we used the NMA on discontinuation due to AEs (Section 5.1.5.) and applied*	The approach to modelling treatment discontinuation in RRMS has been a key discussion topic in the ongoing NICE appraisal of cladribine (GID-TA11293).[29] At the first Committee meeting it was discussed that a broader definition of discontinuation, beyond only AEs, is relevant. The Committee agreed with this approach in the Draft Guidance Consultation i.e., the Committee believes that treatment switching should be reflected in treatment discontinuation rates. Note: the EAG definition of discontinuation in GID-TA11293 is broader still. Additionally, in GID-TA11293 the Committee have suggested using time to next treatment data from CLASSIC-MS to inform the treatment discontinuation for cladribine within the economic evaluation, rather than the CLARITY data.[30]	The approach and assumptions underpinning the modelling of treatment discontinuation should be compared and validated to the ongoing feedback and discussions in GID-TA11293. Where there are differences in the assumptions, it should be highlighted why this is the case and what impact these differences are likely to have on results. The source informing the discontinuation rates for cladribine should be consistent with the ongoing NICE appraisal for cladribine (GID-TA11293).

	treatment effects to the baseline rates from AFFIRM.		
Page 121 (5)	No stopping rule is applied at EDSS 7.	This assumption is inconsistent with UK clinical guidelines, the NHS treatment algorithm, and previously published and ongoing NICE submissions for treatments for MS. The Association of British Neurologists clinical guideline recommends treatment in RRMS to cease once patients are non-ambulatory (i.e. EDSS 7.0).[31] The NHS treatment algorithm states that therapy should be discontinued after the development of inability to walk (EDSS 7.0), persistent for more than 6 months due to MS.[32] Stopping rules are included within the NICE submissions for siponimod (TA656), ponesimod (TA767), ocrelizumab (TA533), alemtuzumab (TA312), and cladribine (TA616 and GID-TA11293).[24,29,33–36]	In line with UK clinical guidelines, the NHS treatment algorithm, and previously published and ongoing NICE submissions for treatments for MS, stopping rules should be applied for treatments from EDSS 7.
Page 121 (1)	*"The event rates were a combination of natural history (informed by analyses of MS registry data described below) and treatment effects"*	There is limited information available on the data obtained from the MS Registry and the interpretation of these data. E.g., what length of follow-up was available in the MS Registry for each of the therapies? Was the length of follow-up impacted by treatment?	Provide more information on the data obtained from the MS Registry and the interpretation of these data.
Page 122 (3)	*"The covariate for treatment is only used to*	There is no justification provided as to why the natalizumab data from the MS Registry was used to inform baseline rates.	Provide justification why the natalizumab data from the MS

	obtain baseline rates specific to natalizumab, to which the NMA hazard ratios were applied"		Registry was used to inform baseline rates, and not another treatment. Provide a narrative for the impact of this selection.
Table 19, page 126 Table 24, page 133	*Utility decrements and costs associated with SAEs from AFFIRM*	Biogen is concerned that only SAEs associated with natalizumab-TYS from the AFFIRM trial are included in the model. While we acknowledge that this is a pragmatic approach, and consistent with previous TAs, it does not take into account the known SAEs associated with other therapies. For example, in 2019 the EMA recommended restricting the use of alemtuzumab due to reports of rare but serious cardiovascular disorders and immune-related disorders.	Provide justification for why only natalizumab-TYS SAEs are included in the economic model
Table 29, Page 141 and Table 8, Page 77	*"The event rates were a combination of natural history (informed by analyses of MS registry data described below) and treatment effects."*	The relative outcomes from the MS Registry presented in Table 29 (page 141) do not align with the mean ranking of interventions from the NMAs presented in Table 8 (page 77). This discrepancy is not discussed within the EAG report.	The validity of outcomes from the MS Registry and the NMA should be discussed. Particularly as these sources provide differing conclusions of relative efficacy. The impact of uncertainties within these data sets on the results should be discussed.
Table 30, Page 141	It is unclear whether the numbers presented in	It would be useful for assessing the validity of the MS Registry and the results informing the model to present both the number of people and the number of events. Additionally, there is no	Further detail and reporting should be provided on the MS Registry including data cuts, cleaning

	Table 30 are number of people or number of events.	narrative on the potential impact of low patient numbers or events on the analysis.	processes (if applicable), inclusion/ exclusion criteria, sample sizes per treatment and follow-up over key timepoints. Clarify whether the numbers presented in table 30 are number of people or number of events and add the missing variable. Provide narrative on the potential impact of low patient numbers or events on the analysis – particularly in relation to the relative outcomes differing from those estimated by the NMA.
Page 117 (5) and Figure 24, Page 120	*Treatment status is a key attribute, and the sequence of treatment is represented in Figure 24*	The available therapies at 2nd, 3rd, and 4th line are presented in Figure 24. However, the text does not explain whether 3rd line and 4th line therapies are modelled as a weighted basket of available treatments or whether subsequent therapies are sampled from the available therapies (and how this sampling is conducted e.g., random sampling with replacement). This information is available within the R-based model. However, it is the Company's view that the assumptions and inputs underpinning the model should be presented in the EAG report.	All assumptions used in the modelling should be stated and justified in the EAG report. All inputs used in the modelling should be presented in the EAG report.

Page 117 (5)	*"patients can progress to SPMS on any line of RRMS therapy and are then assumed to receive an average 'basket' of approved therapies"*	In the report, it is unclear whether there are different risks of progression to SPMS depending on the line of therapy. This information is available within the R-based model. However, it is the Company's view that the assumptions and inputs underpinning the model should be presented in the EAG report.	All assumptions used in the modelling should be stated and justified in the EAG report. All inputs used in the modelling should be presented in the EAG report.
Page 22 (3)	*"Patients who progressed SPMS could experience the events EDSS increase, relapse, SAEs, and death"*	In the report, it is unclear whether EDSS regression is included in the SPMS health state. This is excluded on Page 22 and included on Page 121. This information is available within the R-based model. However, it is the Company's view that the assumptions and inputs underpinning the model should be presented in the EAG report.	All assumptions used in the modelling should be stated and justified in the EAG report. All inputs used in the modelling should be presented in the EAG report.
Page 121 (3)	*"Relapse rates in SPMS were informed by the MS registry analyses and included regression on EDSS severity"*		
Table 25, Page 135	For treatment effects, Table 25 references the NMA Section 5.1.2 – 5.1.5.	It is unclear what assumptions are made where no relative efficacy data are available from the NMAs. This information is available within the R-based model e.g. ofatumumab is assumed equivalent to ocrelizumab for CDP outcomes. It is the Company's	All assumptions used in the modelling should be stated and justified in the EAG report. A fully connected network could be generated by including studies for

		view that the assumptions and inputs underpinning the model should be presented in the EAG report.	teriflunomide as previously commented.
Table 19, Page 126	The utility decrement and duration for PML is assumed to be -0.30 and 365.25, respectively.	It is unclear how these values were selected; the utility decrement and duration for PML differs across the appraisals cited in Table 19. E.g., TA616 and TA312 use -0.2 and apply this only over 93.1 days.	Provide justification why the values from TA767 and TA699 were used rather than TA616 and TA312.
Table 20, Page 126-127	Table 20 reports the proportion of patients treated each year.	It is unclear where these data are sourced from and how it is applied within the modelling. This information is available within the R-based model. However, it is the Company's view that the assumptions and inputs underpinning the model should be presented in the EAG report.	All assumptions used in the modelling should be stated and justified in the EAG report.
Table 20, Page 126-127	Hawton et al is referenced for relapse costs.	There is no detail on the relapse costs used in the model. This information is available within the R-based model. However, it is the Company's view that the assumptions and inputs underpinning the model should be presented in the EAG report.	All assumptions used in the modelling should be stated and justified in the EAG report. All inputs used in the modelling should be presented in the EAG report.
Table 21, page 128	Table 21 reports the annual treatment administration costs	It should be acknowledged that whilst the infusion-based therapies (natalizumab, ocrelizumab and alemtuzumab) have all been assigned the same unit cost for infusion, there is a significant difference between the therapies for both infusion and observation times. • Natalizumab-TYS IV: infusion over approximately 1 hour and patients to be observed for 1 hour after the completion	EAG to amend report to acknowledge differences in infusion and observation times.

		of the infusion. Patients should be observed for the first 12 doses, after which the observation period maybe removed or reduced should no infusion reactions be experienced. Total time: 1-2 hours[11] • Ocrelizumab: infusion over approximately 3.5 hours followed by observation for at least 1 hour after the completion of the infusion. Should a patient not experience a serious infusion-related reaction to any infusion, a shorter 2-hour infusion can be used for subsequent doses. Pre-medications are required prior to each infusion for a duration of 30-60 mins.[37] Total time – 3.5-5.5 hours • Alemtuzumab: infusion over a period of approximately 4 hours. Observation for infusion reactions is recommended for a minimum of 2 hours after infusion. Pre-medications are required immediately prior to the first three infusions in each cycle.[20] Total time: 6 hours	
Table 24, Page 133-134	The cost of PML is assumed to be £14,333.02.	It is unclear how this value was selected the cost for PML differs across the appraisals cited in Table 19. E.g., TA616 used £1,268.11 and TA699 used £1,077.72.	Provide justification why the value assumed is valid, rather than the values from other published appraisals.
Table 25, Page 134-135	There are serious adverse events listed in Table 25 for which no utility or cost data are presented.	It is unclear what impact these serious adverse events have in the model. This information is available within the R-based model. However, it is the Company's view that the assumptions and inputs underpinning the model should be presented in the EAG report.	All assumptions used in the modelling should be stated and justified in the EAG report.
Factual Accuracies in the R-based Model			

Page 126-127, Table 20	In the R-based model, the annual cost of fingolimod is £19,176	In Table 20 (Page 126-127), the annual cost of fingolimod is £19,169.	Clarify the correct number and update throughout.
Page 124, Table 16	In the R-based model, the disutility of relapse SD is 0.013.	In Table 16 (Page 124), the disutility of relapse SD is 0.016.	Clarify the correct number and update throughout.
Remaining Factual Accuracies in the EAG Report			
Page 10 – 14	*"List of Tables"*	The page numbers do not correspond to the position of tables throughout the document.	Update the list of tables.
Page 31 (1)	*"To provide an accurate and reliable evaluation of confirmed disability progression (CDP), two consecutive examinations should be carried out by the same physician at least 6 months apart."*	This statement should also mention the potential for an evaluation of CDP at 3 months, and commentary around a positive 3-month assessment being more likely to be influenced by a recent relapse i.e. a positive 3-month CDP may not be as indicative of permanent disability progression as a CDP conducted at 6 months.	Update the text to include a 3-month CDP

Page 54 (1)	*"This restricted NMA in the general RRMA population was plotted together with results from the equivalent network in the HARRM population for comparison"*	RRMA and HARRM should be RRMS and HARRMS, respectively	To correct typographical errors
Table 7, page 62	*Risk of bias table*	Row that includes the CONFIDENCE study. Cell marked "High" is highlighted the incorrect colour. There is also inconsistency in the shade of orange used to highlight "High" throughout the table	To amend incorrect table shading
Page 71 (1)	*"followed by natalizumab (2.2, 95 % CrI 1, 4; 17%)"*	Mean ranking for natalizumab IV300 is reported as (2.2, 95% CrI 1,4) for ARR on Page 71. In Table 8 (Page 77), this is (2.3, 95% CrI 1, 4).	Clarify which is correct and update the incorrect number.
Page 71 (1)	*"There was greater uncertainty for natalizumab biosimilar which had a 4% probability of ranking first"*	Probability of ranking first for natalizumab biosimilar is reported as 4% for ARR on page 41. In Table 8 (Page 77), this is 5%.	Clarify which is correct and update the incorrect number.
Page 71 (1)	*"This shows that the RR (95% CrI) for natalizumab compared to*	This does not align with the NMA results presented in Table 60 (Page 317; 0.65 (0.34, 1.26)). The 0.65 (0.33, 1.23) comes from the natalizumab vs. natalizumab biosimilar study reported in Table 10 (Page 95). However, Page 71 references the NMA in the text.	Clarify whether the study results or the NMA results should be presented on Page 71 and clarify and/or update.

	natalizumab biosimilar, the key comparison for this appraisal, was 0.65 (0.33, 1.23), suggesting no difference between the ARR for these two interventions."		
Page 80 (2)	*"Figure 5 shows the HR and 95% credible intervals (CrI) for comparison of each intervention included in the network with placebo under the selected random effects model"*	Figure 5 (Page 73) states the HR and 95% credible intervals (CrI) for the fixed effects model – not the random effects model.	Clarify which is correct and update the incorrect text.
Page 81 (2)	*"Figure 6 shows the HR and 95% credible intervals (CrI) for comparison*	Figure 6 (Page 74) states the HR and 95% credible intervals (CrI) for the fixed effects model – not the random effects model.	Clarify which is correct and update the incorrect text.

	of each intervention included in the network with placebo under the selected random effects model"		
Page 83 (2)	*"Ocrelizumab had the highest mean ranking (1.4, 95 % CrI 1, 3) and the greatest probability of ranking first (68%)"*	Table 8 (Page 77) states ocrelizumab has a 0% probability of ranking first for the MRI Gd+ outcome.	Clarify which is correct and update the incorrect text.
Page 83 (2)	*"All other interventions had a 0% probability of ranking first"*	Table 8 (Page 77) states that alemtuzumab has a 68% probability of ranking first.	Clarify which is correct and update the incorrect text.
Page 84 (3)	*"The DIC (26.4 vs 27.9) and residual deviance (14.5 vs 15.6 on 18 data points) were very similar for both fixed and*	In Table 76 (Page 338) the residual deviance is 15.4 vs 15.6.	Clarify which is correct and update the incorrect number.

	random effects models"		
Page 85 (1)	*"Figure 7 shows the hazard ratio (HR) and 95% credible intervals (CrI) for comparison of each intervention included in the network with placebo"*	This paragraph is specific to the time to developing at least one new or enlarging T2 weighted MRI lesions endpoint – with results shown in Figure 8 (Page 76; not Figure 7).	Clarify which is correct and update the incorrect reference.
Page 85 (1)	*"All interventions except interferon beta 1a SC44 were associated with a greater reduction (i.e., HR<1 AND 95% CrI excluding 1.00) in the risk of relapses compared to placebo"*	This paragraph is specific to the time to developing at least one new or enlarging T2 weighted MRI lesions endpoint. This conclusion does not align with the relevant endpoint.	Clarify and update the text.
Page 85 (1)	*"All other interventions had a 0%*	In Table 8 (Page 77), alemtuzumab has a 3% probability of ranking first for the relevant time to developing at least one new or enlarging T2 weighted MRI lesions endpoint.	Clarify and update the text.

	probability of ranking first"		
Page 3 (5), Page 24 (2), and Page 87 (2)	*"any AEs (HR 1.06 (0.77, 1.46)", "There was no evidence of a difference between natalizumab and natalizumab biosimilar 1.06 (0.77, 1.46) in the risk of any AEs", and "This shows that the HR (95% CrI) for natalizumab compared to natalizumab biosimilar, the key comparison for this appraisal, was 1.06 (0.77, 1.46) suggesting no difference between the HR*	Table 80 (Page 344) reports this hazard ratio as 1.06 (0.79, 1.45).	Clarify which is correct and update the incorrect number(s).

	for these two interventions"		
Page 90 (2)	*"Results were very similar for both random and fixed effects models (Table 82in Appendix 5)"*	This text is specific to the discontinuation due to AEs endpoint – with results shown in Table 85 (page 350). Not Table 82.	Clarify and update the reference.
Table 10, Page 95	*"Data on Natalizumab and Natalizumab biosimilar" column*	The source of data in this column is unclear. CP3, CP6, and MRI hazard ratios align with the results from the NMA tables in the Appendices. However, the hazard ratios presented for ARR, any AEs, and treatment related AEs do not align with the NMA. • ARR reported as 0.65 (0.34 – 1.26) from the NMA. • AEs reported as 1.06 (0.79 – 1.45) from the NMA. • Treatment related AEs, an NMA was not conducted.	Clarify the source of data in Table 10 and either add references or update in line with the NMA results.
Page 98 (3)	*"The heterogeneity standard deviation estimated by the random effects model (tau (95% CrI) of 1.40 (0.05, 3.95) in Table 59) was high when compared to the average treatment effect*	This text is specific to the ARR endpoint in the HARRMS population. Table 59 (Page 315) shows the results of the RRMS population and the numbers do not align with the text. Table 88 (Page 354) shows the relevant numbers from the text for the ARR endpoint in the HARRMS population.	Clarify and update references.

	on the log rate ratio scale (-0.58 in Table 59)"		
Table 19, Page 126	The utility decrement of -0.07 and duration (days) of 24.5 for gastritis are referenced from TA616.	In the publicly available documents from TA616, these numbers could not be matched. 24.5% was reported as the probability of the event.	Clarify source of the inputs for gastritis and any assumptions required.
Table 4 (Page 42-43), Table 20 (Page 126-127), and Table 21 (Page 128-129)	The dosing information presented across these tables is inconsistent.	The dosing information presented across these tables is inconsistent. • In Table 4 (Page 42-43) ofatumumab states 20mg every 4-weeks as an SC. However, Table 20 (Page 126-127) states 50mg 15 times a year. • In Table 4 (Page 42-43) alemtuzumab states 12mg for 5-days in month 1, then 3-days in month 12. In Table 20 (Page 126-127) and Table 21 (Page 128-129) this states five in the first year, then three in the following year. • In Table 21 (Page 128-129), unclear why some oral therapies have costs and others do not e.g., ponesimod, cladribine, and fingolimod.	Clarify which dosing schedule is correct and ensure consistent throughout report and model.
Table 4 (Page 42-43), Table 20 (Page 126-127), and Table 21 (Page 128-129)	Alemtuzumab re-treatment is not included within the economic evaluation.	In addition to the discrepancies between Table 4 (Page 42-43), Table 20 (Page 126-127) and Table 21 (Page 128-129) for alemtuzumab administration (see row above), the economic evaluation does not include rates of alemtuzumab re-treatment. Alemtuzumab re-treatment is relevant to UK clinical practice and rates were implemented in the base case in the NICE submissions for alemtuzumab (TA312) and for the alemtuzumab	In line with UK clinical practice and previous NICE appraisals, alemtuzumab re-treatment should be included in the base case.

		comparator in the ocrelizumab appraisal (TA533).[24,33] In these appraisals, the rates of re-treatment were informed by the CARE-MS I, CARE-MS II and CAMMS233 clinical data.[38–40] In both NICE appraisals, clinical experts confirmed the use of alemtuzumab re-treatment for some patients in UK clinical practice.	
Page 127, Table 20	A row is included for natalizumab SC biosimilar.	The SC form of the natalizumab biosimilar does not exist.	Remove row and mention of the natalizumab SC biosimilar throughout.
Page 129 (3) Page 135 (1)	"Patients progressing on to SPMS are treated with Peginterferon beta 1a or Siponimod." "Patients who discontinue treatment are allowed to switch onto one of the higher line treatments. Patients who progress on to SPMS are assumed to be treated with Siponimod or	Factually inaccurate in both sections, “Peginterferon beta 1a” should be replaced with “beta-interferon”. Peginterferon beta 1a does not have marketing authorisation to treat SPMS.	Amended text as suggested

	Peginterferon beta 1a for the remainder of their time in the model."		
Page 133 (1)	*"The costs have been inflated to 2022/2023 prices using the NHSCII pay and prices index, details provided in Table 23"*	On Page 126 (Paragraph 2), it states all costs inflated to 2023/24.	Clarify the correct cost year and update throughout.
Page 134, Table 25	The estimate reference reported for the initial EDSS distribution is Table 26.	The EDSS initial distribution is presented in Table 28 – not Table 26.	Clarify and update references.
Page 135, Table 25	The estimate reported for the standardised mortality ratio is: "HR 1.68 (95%CI: 2.05-1.38)"	This should be 1.68 (1.38 – 2.05).	Update the text.
Page 135, Table 25:	The estimates reported for the SMR by EDSS	In Pokorski et al. these values are 1.6, 1.84, and 4.44.	Clarify whether 4.4 or 4.44 was used in the modelling. If 4.4 was used, update using the 4.44 in the

	are 1.6, 1.84, and 4.4.		document and model as per the publication.
Page 138, Table 27	"Uses HA RRMS from MS Registry for baseline rates, all RRMS fixed effects from NMA for treatment effects, EDSS starting distribution from MS Registry for HA RRMS"	The model uses data from all RRMS for EDSS regression baseline rates.	Clarify and update text.

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Multiple Technology Appraisal

Natalizumab and Tyruko (natalizumab biosimilar) for treating highly active relapsing-remitting multiple sclerosis after at least one disease modifying therapy [ID6369]

External Assessment Group Report consultation response form

As a stakeholder you have been invited to comment on the External Assessment Group (EAG) Report for this appraisal.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

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The deadline for comments is **5pm** on **08 January 2025**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF). Thank you for your time.

About you

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Sandoz
Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	**Manufacturer of Tyruko (natalizumab biosimilar)**
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry	**None**

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Comments on the External Assessment Report

Comments on External Assessment Report
Summary • Sandoz thanks NICE for the opportunity to review the EAG report, several aspects of which are of concern: ○ **Comparator Treatments**: Natalizumab is a high-efficacy treatment for highly active RRMS; the most relevant comparators are ofatumumab and ocrelizumab, not older DMTs. Sandoz requests NICE to focus on realistic clinical comparisons. ○ **Drug Prices**: The AG report uses list prices instead of confidential discounted prices for economic analyses, potentially misleading readers. Sandoz requests conclusions drawn from true NHS prices. ○ **Extended Interval Dosing**: Natalizumab can be administered in extended intervals, which may affect cost-effectiveness outcomes. Sandoz requests analysis on this dosing regimen. ○ **Cost of Intravenous Administration**: Sandoz notes discrepancies in administration costs between the AG report and NICE budget impact tests and requests alignment. ○ **Biosimilar Treatment**: The AG report treats natalizumab biosimilar as a separate clinical product. Sandoz argues it should only differ in price from the originator in the economic analysis. ○ **Company Submissions**: Sandoz note that their submission on comparator and cost comparison methodology appeared largely not to have been considered and seeks full consideration of the arguments put forth within it. ○ **AG NMA Connectivity**: The AG's network meta-analysis disconnects some high-efficacy treatments. Sandoz suggests using a published NMA for better connectivity. ○ **Mortality Assumptions**: The AG assumes consistent mortality risk across all disease severity stages, which Sandoz finds implausible and suggests using recent UK cohort data instead. ○ **Cost of Serious Adverse Events**: Sandoz questions the validity of cost inputs for adverse events in the AG report and requests reassessment. ○ **Cost of JCV Testing**: Sandoz provides JCV testing services and disputes the AG's claim about limited access in the NHS, requesting the exclusion of these costs from analyses.

Issue 1: Comparator treatments likely to be displaced if natalizumab reimbursement extended to HA RRMS

- Natalizumab is a monoclonal antibody DMT classed as a drug of high efficacy (average relapse reduction substantially more than 50%) as per ABN guidelines. Natalizumab would therefore be used in patients for whom a high efficacy biologic treatment is considered the most appropriate treatment approach on the balance of benefit–risk in the context of the patient need. This is reflected in ABN guidelines, which state that "alemtuzumab and natalizumab are appropriate where individuals and their multiple sclerosis specialist neurologists are most concerned to achieve high efficacy, despite the more complex safety profile compared to Category 1 drugs".
- Alternative licensed high-efficacy biologic treatments other than natalizumab are ocrelizumab and ofatumumab (both licensed after the 2015 ABN guidelines were published) and alemtuzumab; therefore, these represent the treatment options that would represent the most relevant treatment choice alternatives to natalizumab in clinical practice. However, alemtuzumab is associated with a specific and complex safety profile that has restricted its use in UK clinical practice, and Sandoz understands that alemtuzumab has limited usage in practice as a treatment option among patients with 'highly active' RRMS. As such, ofatumumab and ocrelizumab represent the most relevant comparators to natalizumab for patients with highly active disease after at least one DMT.
- The other comparator treatments considered in the AG analysis are not relevant comparators in clinical practice as they are not 'high efficacy' biologic treatments and would therefore generally be used in a different patient-specific clinical context to natalizumab. Sandoz further note that the NHS England treatment algorithm for DMTs does not list older DMTs such as GA and the IFNs as escalation options following disease activity on first- or second-line treatment, as such the broad NICE scope for this appraisal is misaligned with NHS clinical practice.
- Whilst Sandoz acknowledge the need for the AG to address the full NICE scope for the purposes of following NICE process, they are disappointed that the interpretation and conclusions have not focussed on the realistic clinical comparison to similarly efficacious DMTs.
- Sandoz request that NICE direct the AG to present scenario analyses to the Appraisal Committee Meeting covering (a) the limited comparator list proposed by Sandoz using the AG model; (b) the limited comparator list proposed by Sandoz using the cost comparison methodology proposed by Sandoz in their submission to this appraisal; (c) the limited comparison list included in the NHS England treatment algorithm for escalation following activity on first- and second-line DMTs, using the AG model. Sandoz anticipate that these analyses will demonstrate a material impact on the cost-effectiveness estimates.

Issue 2: Drug prices used in the economic analysis

- While the AG report mentions the existence of confidential discounts for both interventions and most comparators initially, it then omits to remind the reader of this in all subsequent analyses, and has produced a Report that draws conclusions from an economic analysis that has knowingly been conducted on prices which are not relevant (i.e. list prices). These conclusions may therefore easily mislead the reader.
- Whilst Sandoz strongly appreciate the necessity for commercial confidentiality of the prices themselves, they request that explicit mention of the analyses at true prices be added to the report and conclusions drawn to the extent that is compatible with maintaining confidentiality; at a minimum the reader must be clearly reminded that the true conclusions on cost-effectiveness will be drawn from confidential prices only and not from the presented EAG analysis. Sandoz note that such conclusions are routine in NICE STA appraisals to allow public understanding of the appraisal process.
- Additionally, Sandoz note that the price of their product has recently been updated following NHS England's latest pricing review of natalizumab biosimilar and request that this most up to date price be included in the analyses presented to the Appraisal Committee Meeting. Sandoz anticipate that these analyses will demonstrate a material impact on the cost-effectiveness estimates.

Issue 3: Omission of extended interval dosing

- Sandoz note that the SmPC for each natalizumab product provides the option for "extended interval dosing", whereby patients receive six-weekly administrations of natalizumab rather than the standard four-weekly dose. Sandoz request that the AG produce economic analyses that consider some proportion of patients to follow this regimen.
- As laid out in the submission by Sandoz to this appraisal, based on clinical opinion sought by Sandoz, in one centre in the UK approximately 25% of patients received EID dosing. The SPC for natalizumab notes that "in anti-JCV antibody positive patients, extended interval dosing of natalizumab (average dosing interval of approximately 6 weeks) is suggested to be associated with a lower PML risk compared to approved dosing."
- The issue of extended interval dosing is likely to have a material impact on the cost-effectiveness estimates and Sandoz request that this issue is discussed in full at the Appraisal Committee Meeting, and therefore request that NICE ensure that the AG are directed to produce meaningful economic analyses on this point prior to the Appraisal Committee Meeting.

Issue 4: Cost of intravenous administration

- Sandoz note that the cost quoted by the AG for intravenous administration, is materially higher than that used by the NICE budget impact test even though both use currency code AA30F; given the importance of administration cost as a driver of the overall cost of natalizumab, Sandoz request that NICE direct the AG to align to the BIT cost used, as accepted by NICE and NHS England.

Issue 5: AG inappropriately model natalizumab biosimilar as a clinically separate product to the originator

- Sandoz are concerned that the AG Report treats the natalizumab biosimilar product as a separate clinical product to the originator product, rather than assuming the biosimilar differs only in price. Any clinical data are inherently from small studies focussed on meeting the needs of the biosimilar regulatory process, putting a biosimilar at a disadvantage if it is treated as a separate clinical product in an appraisal.
- Given the NICE position statement on biosimilars, wherein any approval for an originator product automatically applies to all future biosimilars, Sandoz request that NICE direct the AG to treat biosimilar natalizumab as differing only in price. As such Sandoz request that the AG report be amended to remove all interpretations and conclusions and other statements which are predicated on assuming a clinical difference between originator and biosimilar. In addition, all economic analysis must be amended such that the biosimilar differs from the originator only with respect to costs.

Issue 6: Company submissions and cost comparison methodology

- Sandoz made a submission in good faith. We believe we have a reasonable expectation that our submission will be given due consideration by the AG. This appears not to be the case. This reduces our confidence that the consultation process adequately responds to consultee views. The risk is that the committee publishes guidance based on incomplete information. We urge NICE and the AG to reconsider the company submissions

Issue 7: AG NMA connectivity in the main RRMS analyses

- Sandoz note that defects in the AG NMA resulted in one of the key high efficacy DMTs, ofatumumab, being disconnected in some analyses, and minimally connected in others.
- Sandoz, in their submission to this appraisal, provided citation to a recent high quality NMA of DMTs which shows that a properly connected network of all DMTs, including ofatumumab, can be undertaken with the inclusion of all licenced DMTs. Sandoz note that the AG have correctly included teriflunomide in their network, even though it is not within the scope for this appraisal, because it is a comparator in the ofatumumab trials. Sandoz note that if the AG had taken care to include all DMT trials in their main RRMS network, including those for teriflunomide and DMF, their NMA would become better connected and more robust.
- Rather than spend time updating the AG NMA, Sandoz request that the published NMA cited in their submission be presented to the Appraisal Committee Meeting as an alternative and more appropriate source of relative effectiveness estimates.

Issue 8: AG mortality assumptions in the economic analysis

- Mortality in RRMS relative to the general population is well recognised to increase at more severe stages of the disease, however the AG have implausibly modelled that the relative risk of death is equal from EDSS 1 to EDSS 9.
- Sandoz recognise the criticisms of the most commonly used source of mortality inputs for prior appraisals, but would contend that assuming an equal risk across disease severity is more implausible than applying outdated risks.
- Sandoz would note that a relatively recent analysis of a UK cohort is available in the literature, which again finds that mortality risk increases with EDSS:
    - Harding, Katharine et al. A contemporary study of mortality in the multiple sclerosis population of southeast Wales. Multiple Sclerosis and Related Disorders, Volume 25, 186 - 191
- Given the results of the AG scenario analyses, it appears that this assumption may demonstrate a material impact on the cost-effectiveness estimates.

Issue 9: Cost of serious adverse events in the AG model

- The values of many of the inputs in Table 24 of the AG Report appear to lack face validity, including £7k for a urinary tract infection, £21.5k for 52 face-to-face consultant appointments for depression, and the use of lower respiratory tract infection costs for anaphylaxis.
- Sandoz requests that all inputs in Table 24 are reconsidered for face validity.

Issue 10: Cost of JCV testing

- Sandoz provide a JCV testing service for the NHS and can confirm that a large number of tests (more than [redacted] to date) have been provided under this service; Sandoz are not aware of any difficulties in the NHS accessing their funded testing service.
- Similarly, Sandoz are aware of the JCV testing service provided by the manufacturer of natalizumab originator, and are unaware of any difficulties in the NHS accessing it.
- Given this, Sandoz consider the advice given to the EAG that funded JCV testing is not widely available to be inaccurate and request that the Appraisal Committee meeting be presented with economic analysis that exclude the cost of JCV testing from the model.

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Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

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About you

NICE National Institute for Health and Care Excellence

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Association of British Neurologists
Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	In the past 12 months, the ABN has received sponsorship from the following companies to support the ABN Annual Conference. Sponsorship companies have no editorial input, control over the agenda, speaker selection, content development nor opportunity to influence the conference. Sponsorship is £18,020 per company. • Abbvie • Alnylam • Angelini • argenx • Biogen • Eisai • Eli Lilly • Janssen • Pfizer • Roche • Sanofi • Teva • UCB

Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry	**Nil**

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Comments on the External Assessment Report

Comments on External Assessment Report
We note that the conclusion of the EAG report is that natalizumab is not cost effective compared to comparators (other than ocrelizumab) for the treatment of highly active MS. This conclusion is entirely based on cost rather than efficacy, as in the analysis presented natalizumab is consistently highly likely to be among the most effective treatments. We would like to raise the following points:
• Whilst natalizumab is not the most cost effective in the analysis, there was no difference in QALYs with 95% CI completely overlapping. If natalizumab is equivalent to any other DMT in terms of cost effectiveness then we should be able to offer patients this choice, as on efficacy in the NMA it consistently ranks within the top 2 across a range of measures. Further, six-weekly natalizumab dosing is now widespread across the NHS, which reduces cost over the course of a calendar year (average 13.5 doses with 4 weekly administration vs 9 doses with extended interval dosing) alongside mitigating some of the PML risk and costs associated with this rare complication. • The cost of John Cunningham human polyomavirus (JCV) testing was included for both natalizumab and natalizumab biosimilar as clinical advice was that the manufacturer scheme of paying for JCV testing is not widely available. We would argue that this assumption is flawed. At present, we only use the manufacturer scheme – there is no NHS test that has demonstrated equivalence of results that allows us to risk stratify in a way that guides clinical practice in terms of monitoring and risk mitigation. • This report by definition is purely based on cost effectiveness and does not consider equalities issues related to protected characteristics. Natalizumab has a well-established safety profile in pregnancy and denying women with highly active MS the opportunity to switch onto this therapy means that those with breakthrough disease or adverse events on first line therapy such as ocrelizumab are forced to switch to a therapy of lower efficacy given the teratogenic considerations around other treatments.

NICE National Institute for Health and Care Excellence

Multiple Technology Appraisal

Natalizumab and Tyruko (natalizumab biosimilar) for treating highly active relapsing-remitting multiple sclerosis after at least one disease modifying therapy [ID6369]

External Assessment Group Report consultation response form

As a stakeholder you have been invited to comment on the External Assessment Group (EAG) Report for this appraisal.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

The deadline for comments is **5pm** on **08 January 2025**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).Thank you for your time.

About you

NICE National Institute for Health and Care Excellence

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Merck Serono
Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	**Not applicable**
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry	**None**

Comments on the External Assessment Report

Comments on External Assessment Report
Incorrect information about cladribine Throughout the External Assessment report, Merck Serono have noticed inconsistencies and mistakes regarding the evidence and data for cladribine tablets. Some of these inconsistencies, especially regarding the data informing the NMA have greatly impact the NMA results, leading to misleading conclusions regarding the comparative efficacy of cladribine tablets. Please see below a list of errors we identified: **<u>Serious adverse events (SAEs)</u>** **pg. 24:** In the EAG report, it has been mistakenly stated that no data were available for cladribine for SAEs. In the pivotal CLARITY study by Giovannoni et al 2010, SAEs for cladribine have been reported (*Giovannoni, G., Comi, G., Cook, S., Rammohan, K., Rieckmann, P., Sørensen, P.S., Vermersch, P., Chang, P., Hamlett, A., Musch, B. and Greenberg, S.J., 2010. A placebo-controlled trial of oral cladribine for relapsing multiple sclerosis. New England Journal of Medicine, 362(5), pp.416-426.)* **Pg.307, Table 55:** It has been mistakenly stated that no SAEs were reported for cladribine. In the pivotal CLARITY study of Giovannoni et al 2010, SAEs for cladribine have been reported (*Giovannoni, G., Comi, G., Cook, S., Rammohan, K., Rieckmann, P., Sørensen, P.S., Vermersch, P., Chang, P., Hamlett, A., Musch, B. and Greenberg, S.J., 2010. A placebo-controlled trial of oral cladribine for relapsing multiple sclerosis. New England Journal of Medicine, 362(5), pp.416-426.)* Based on the above, the NMA should be revised, and results should be updated throughout the report. **<u>6-month CDP of cladribine versus placebo NMA results</u>** **Pg.74:** In Figure 6, the hazard ratio (HR) and 95% confidence (CI) for cladribine reported in the fixed effects NMA seems incorrect. The HR (95% CI) from the CLARITY study is 0.53 (0.36-0.79) as reported in Figure 2 from the post-hoc analysis of the CLARITY study by Giovannoni et al. 2018. (*Giovannoni, G., Soelberg Sorensen, P., Cook, S., Rammohan, K.W., Rieckmann, P., Comi, G., Dangond, F., Hicking, C. and Vermersch, P., 2019. Efficacy of Cladribine Tablets in high disease activity subgroups of patients with relapsing multiple sclerosis: A post hoc analysis of the CLARITY study. Multiple Sclerosis Journal, 25(6), pp.819-827.)* Therefore it seems highly unlikely that this NMA could result in such a drastically different HR for

time to CDP6 for cladribine vs. placebo compared to the CLARITY Phase III study. This result is also misaligned with reported HRs for CDP6 for cladribine vs. placebo in previously published network meta-analyses (Siddiqui, M. K., Khurana, I. S., Budhia, S., Hettle, R., Harty, G., & Wong, S. L. (2017). Systematic literature review and network meta-analysis of cladribine tablets versus alternative disease-modifying treatments for relapsing–remitting multiple sclerosis. Current Medical Research and Opinion, 34(8), 1361–1371).

Pg. 104, Table 12: HRs and 95% CrI for the HARRMS population for cladribine against placebo reported in this section are incorrect. In the HARRMS population, CPD6 should be 0.18 (0.08-0.44) as reported in Giovannoni et al. 2018. (*Giovannoni, G., Soelberg Sorensen, P., Cook, S., Rammohan, K.W., Rieckmann, P., Comi, G., Dangond, F., Hicking, C. and Vermersch, P., 2019. Efficacy of Cladribine Tablets in high disease activity subgroups of patients with relapsing multiple sclerosis: A post hoc analysis of the CLARITY study. Multiple Sclerosis Journal, 25(6), pp.819-827.)*

Pg. 104, Table 12, Pg.300, Table 51 and Pg.303, Table 52: It has been incorrectly stated that HRs and 95% CI for CDP6 for cladribine against placebo are not reported. As presented in the study of Giovannoni et al. 2018., the CDP6 of cladribine versus placebo is 0.53 (0.36-0.79) as shown in Figure 2 of the paper. (*Giovannoni, G., Soelberg Sorensen, P., Cook, S., Rammohan, K.W., Rieckmann, P., Comi, G., Dangond, F., Hicking, C. and Vermersch, P., 2019. Efficacy of Cladribine Tablets in high disease activity subgroups of patients with relapsing multiple sclerosis: A post hoc analysis of the CLARITY study. Multiple Sclerosis Journal, 25(6), pp.819-827.)*

Based on the above, the NMA should be revised and results should be updated throughout the report.

3-month CDP of cladribine versus placebo

Pg. 104, Table 12: For HARRMS, CDP3 for cladribine tablets versus placebo should be 0.28 (0.15-0.54) as reported in the Supplementary Figure 1 in Giovannoni et al. 2018. Additionally, for the general RRMS population, CDP3 for cladribine tablets versus placebo should be 0.59 (0.43-0.82) as reported in the Supplementary Figure 1 in Giovannoni et al. 2018. (*Giovannoni, G., Soelberg Sorensen, P., Cook, S., Rammohan, K.W., Rieckmann, P., Comi, G., Dangond, F., Hicking, C. and Vermersch, P., 2019. Efficacy of Cladribine Tablets in high disease activity subgroups of patients with relapsing multiple sclerosis: A post hoc analysis of the CLARITY study. Multiple Sclerosis Journal, 25(6), pp.819-827.)*

MRI outcomes

Pg. 82: In the report, it is stated that "*Data were only available for T2 lesions for interferon beta 1a (SC22) and so this was only included for this outcome".* Merck Serono would like to clarify that relevant data for cladribine tablets are reported on the Supplementary Files in Giovannoni et al. 2018 and in Table 2 of Giovannoni et al 2010. (*Giovannoni, G., Soelberg Sorensen, P., Cook, S., Rammohan, K.W., Rieckmann, P., Comi, G., Dangond, F., Hicking, C. and Vermersch, P., 2019. Efficacy of Cladribine Tablets in high disease activity subgroups of patients with relapsing multiple sclerosis: A post hoc analysis of the CLARITY study. Multiple Sclerosis Journal, 25(6), pp.819-827; Giovannoni, G., Comi, G., Cook, S., Rammohan, K., Rieckmann, P.,*

Sørensen, P.S., Vermersch, P., Chang, P., Hamlett, A., Musch, B. and Greenberg, S.J., 2010. A placebo-controlled trial of oral cladribine for relapsing multiple sclerosis. New England Journal of Medicine, 362(5), pp.416-426.)

Pg.304, Table 53: Merck Serono is unclear which CLARITY trial publication was used to extract proportion of patients with lesions on MRI for cladribine tablets. We would like to refer the EAG to the Supplementary Table 1 of Giovannoni et al. 2018

Cost-effectiveness model of cladribine

Pg. 114: The report stated incorrectly that the model used for TA616 "*simulates a cohort of patients over a lifetime progressing through 10 RRMS & 10 SPMS EDSS health states leading up to death."* Please note that in TA616, the structure of the model comprised 11 health states: 10 Expanded Disability Status Scale (EDSS) states and a single state for death from all causes.

Pg. 358, Table 91: Similarly, in Table 91, under the column 'outcomes and sources of data' for TA616, it has mistakenly been reported that *"Converting from RRMS to SPMS from the London, Ontario MS database supplemented by the EXPAND trial."* Please note that this was not the case in TA616, as only 11 health states were reported and no SPMS states were included. Therefore, this information is inaccurate.

Pg. 326, Table 92: Information regarding TA616 should be revised based on the previous comments.

In addition, it was also indicated incorrectly that in TA616, no treatment waning was applied: "*treatment discontinuation as a proxy to waning to as in previous appraisals."* Equal waning of treatment effectiveness for cladribine and all comparators was applied in the model submitted for TA616.

Costs of cladribine

Pg 127, Table 20: The annual treatment acquisition cost for cladribine is incorrectly reported. The annual treatment cost should be £25,953 as the cost of cladribine is dependent on the weight of the cohort, with dosing based on a target dose in milligrams per kilogram per dose. The dose of cladribine tablets is modelled based on the weight distribution of the cohort multiplied by the number of tablets needed to treat people within each weight class.

Pg 130, Table 22: The resource use for cladribine tablets in Year 2 onwards is incorrect. This should be revised to reflect: 1 neurology visit instead of 3 neurology visits as per the NHS clinical practice and as indicated in the TA616 Committee papers. (https://www.nice.org.uk/guidance/ta616/evidence/committee-papers-for-ta493-pdf-7021081261)

Baseline characteristics for HARRMS population

Pg 287, Table 46: Merck Serono is unclear which publication was used to extract data on baseline participant details for the HARRMS population in CLARITY since the reference reported does not include information for the HARRMS population. We would like to refer the EAG to the Supplementary Table 1 of Giovannoni et al. 2018 (*Giovannoni, G., Soelberg Sorensen, P., Cook, S., Rammohan, K.W., Rieckmann, P., Comi, G., Dangond, F., Hicking, C. and Vermersch, P., 2019. Efficacy of Cladribine Tablets in high disease activity subgroups of patients with relapsing multiple sclerosis: A post hoc analysis of the CLARITY study. Multiple Sclerosis Journal, 25(6), pp.819-827).*

Definition of relapse

Pg. 290, Table 47: In the table the definition of relapse from the CLARITY study is incorrect. Based on Giovannoni et al. 2011 and on clincaltrials.gov, a qualifying relapse was defined as: "A qualifying relapse was defined as an increase of 2 points in at least one functional system of the expanded disability status scale (EDSS) or an increase of 1 point in at least two functional systems (excluding changes in bowel or bladder function or cognition) in the absence of fever, lasting for at least 24 hours and to have been preceded by at least 30 days of clinical stability or improvement, which is the definition you have." Therefore, the table under the EDSS column should be updated to: "EDSS increase >2 points in at least one functional system or an increase >1 point in at least at least two functional systems (excluding changes in bowel or bladder function or cognition)".

Relapse rates for cladribine

Pg. 297, Table 49: In Table 49, Merck Serono is unclear which publication was used to extract the relapse rates (95%CI) for both cladribine and placebo. As per the notes under the table "unshaded indicates studies that did not report CIs." However, for cladribine tablets CIs in the table are reported.

HRQoL for cladribine

Pg. 311, Table 57: In Table 57, can the EAG clarify where these data were extracted from.

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About you

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Novartis Pharmaceuticals UK Ltd
Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	**None**
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry	[redacted]

	[redacted]

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Comments on the External Assessment Report

Comments on External Assessment Report
<u>Page 128, Paragraph 2:</u> **"However, our clinical advisors explained that in practice patients do not see differences between SC and IV in intensity of resource use. Beta interferons and Ofatumumab are self-administered injections requiring nurses' time to train patients."** • **Statement that patients do not see differences between SC and IV intensity of resource is misleading as patients would only require 1 x NHS resource utilisation in initiation & ongoing administration of Ofatumumab.** • **Expansion of the nurse time required to deliver the first dose observation of Ofatumumab is not highlighted and differentiated from Beta Interferons.**
<u>Page 128, Table 21:</u> **Annual treatment costs are misleading and overstated – Year 1 and Year 2 onwards state 3 hours of Nurse time (Band 7). NHS resource utilisation, as defined within the Ofatumumab SmPC, requires nurse observation in relation only to the first dose of the initiation and does not require nurse time in Year 2 or beyond.**

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External Assessment Group Report response to comments

Biogen Comments

Page No. (Paragraph)	Related Text	Company Comment	Resolution	EAG response
Full report	Not applicable	Biogen would like to thank the Expert Advisory Group (EAG) for their thorough and detailed assessment of the decision problem. Below is a summary of our feedback on the draft report, including requests for further detail, particularly regarding the MS Registry analyses and outputs from the economic model, and suggestions for updates to address aspects of the value of natalizumab-TYS that have not been fully documented or were excluded from the base case of the economic evaluation. To fully and robustly reflect the value of natalizumab-TYS, we believe that the	To update the report, base case and key sensitivity analyses as described	We greatly appreciate the close feedback provided by the stakeholder. See more detailed responses below

Page No. (Paragraph)	Related Text	Company Comment	Resolution	EAG response
		updated base case and key sensitivity analyses should include: 1. **Cost savings associated with natalizumab SC:** The base case should reflect the Biogen-funded natalizumab-TYS SC home injection service,[1] and the cost, time efficiency, reduced patient burden and patient preference improvements provided by natalizumab-TYS SC compared with IV (see pages 5–7 for further details). 2. **Biogen-funded JCV testing:** The base case should be updated to reflect that JCV testing is nationally available for natalizumab-TYS, funded by Biogen. and to remove costs associated with JCV testing from the natalizumab-TYS (IV & SC) (see pages 7–9 for further details).[2] 3. **Extended interval dosing (EID) for natalizumab:** EID, administering natalizumab-TYS IV or SC Q6W or Q8W instead of SID Q4W should be included as a key sensitivity analysis. EID is used in clinical practice for some UK patients,[3,4] and provides other benefits for patients and the		

Page No. (Paragraph)	Related Text	Company Comment	Resolution	EAG response
		NHS (see pages 9–10 for further details). 4. **Tender pricing:** Drug acquisition costs in the base case economic analysis should be updated to reflect those paid by the NHS in routine practice, namely those associated with procurement via national tender processes (see pages 10–11 for further details). 5. **Comparators:** Based on the NHS England DMT algorithm presented in the CS and the EAG report, the appropriate comparators for the base case for the economic analysis are ofatumumab, ponesimod and cladribine (see pages 11–13 for further details). 6. Remaining factual accuracies in the EAG report and the R-based model: these are detailed in the table below		
General comments and preferred base case/key sensitivity analyses				
Full report	Not applicable	The external validity of the model has been challenging to assess, as many key clinical outputs are not presented within the report. While we ran the model for 100 iterations using the code	Provide key clinical outcomes predicted by the model for transparency and such that these outcomes can be externally validated,	Not feasible within timeline but have responded to identified mortality issue below.

Page No. (Paragraph)	Related Text	Company Comment	Resolution	EAG response
		shared (without making any edits), our observations raised validity concerns regarding the age at death, the duration of time spent in EDSS health states, and the duration on treatment at each line of therapy. These outputs appear inconsistent with expectations – as described in detail below. However, it would be more informative to have these outputs directly from the EAG's original analysis to facilitate a thorough assessment. This would enhance transparency and provide a stronger basis for evaluating the model's validity.	including (non-exhaustive) the age of death, duration of time spent in EDSS health states, and the duration on treatment at each line of therapy.	
Subcutaneous natalizumab-TYS – value and administration costs				
Page 128 (3)	*"The manufacturers anticipate cost savings associated with the administration and monitoring of Natalizumab Sub Cutaneous (SC) in comparison to the intravenous (IV) deliver. However, our clinical advisors explained that in*	This statement is inconsistent with published evidence, which demonstrates clear differences in the costs and benefits accrued to the healthcare system between natalizumab SC and IV administration. Silingardi et al. (2023), as described on page 55 of the CS, report a time and motion study conducted in Salford, an outpatient department of the tertiary neurology service in Greater Manchester that provides DMT treatment for patients with MS.[5] The study found that natalizumab SC significantly reduced	The base case should remove the administration costs associated with natalizumab-TYS (SC) to reflect the demonstrated cost savings associated with natalizumab SC compared to natalizumab IV. The report should acknowledge that these benefits extend beyond	This was following our independent clinical advice. Note that " Scenario 5 (base case & assuming a reduction in Natalizumab-SC administration costs)" explored this and found no impact on conclusions.

Page No. (Paragraph)	Related Text	Company Comment	Resolution	EAG response
	practice patients do not see differences between SC and IV in intensity of resource use."	workload and increased available staff and chair time, with total time savings of 1 hour and 32 minutes per patient compared to natalizumab IV administration. These findings are corroborated by cost-analyses conducted in Spain and Italy, which showed that cost savings associated with natalizumab SC were largely driven by reduced administration costs and increased patient and caregiver productivity, as described on pages 51–52 of the CS.[6,7] Furthermore, this statement does not consider the Biogen-funded natalizumab SC home injection service. This service allows patients to receive their natalizumab SC injections at home, thereby reducing the need for hospital visits. The service includes the delivery of the medicine directly to patients' homes and administration by a Biogen-funded homecare nurse, providing additional cost and potential VAT savings to the NHS.[1] Patient preferences further highlight the value of natalizumab SC. In the NOVA (Part 2) study, the majority of participants on Q6W dosing preferred SC administration over IV, with 82.9% citing "requires less time in clinic" as a key reason for	those captured by the economic evaluation.	

Page No. (Paragraph)	Related Text	Company Comment	Resolution	EAG response
		their preference.[8] Similarly, the TONIC study highlighted that all but one patient who switched from IV to SC expressed either a "fairly strong" or "very strong" preference for natalizumab SC compared to natalizumab IV driven by time savings.[9] These findings are corroborated by the published SISTER (Subcutaneous: Non-Interventional Study for Tysabri Patient Preference – Experience from Real World) study indicated a strong trend toward patient preference for the SC route over the IV route.[10] As well as reducing burden on NHS by freeing up nursing and infusion chair time, natalizumab SC has important benefits in reducing the burden on patients through enabling care closer to home. This minimises the travel and treatment time for patients, helping to address health inequalities and reduce associated patient costs, such as transportation, childcare, and lost productivity due to time away from work. The demonstrated differences in costs, time efficiency, patient burden, and overall preference underline the importance of recognising the broader benefits of natalizumab SC over IV administration. These factors are supported by		

Page No. (Paragraph)	Related Text	Company Comment	Resolution	EAG response
		robust evidence and should be reflected in the economic evaluation.		
JCV testing				
Page 22 (4)	*"The cost of John Cunningham human polyomavirus (JCV) testing was included for both natalizumab and natalizumab biosimilar as clinical advice was that the manufacturer scheme of paying for JCV testing is not widely available"*	At multiple points throughout the report it is stated that JCV testing for natalizumab-TYS and biosimilar is not widely available. This is factually inaccurate for natalizumab-TYS, for which JCV testing is available and funded in the UK for all patients being considered for treatment with natalizumab-TYS.[2] Biogen funded [redacted] Stratify JCV tests between Jan 2024 and Nov 2024 for patients being considered for natalizumab-TYS.	To update the report to reflect that JCV testing is nationally available for natalizumab-TYS, funded by Biogen. and to remove costs associated with JCV testing from the natalizumab-TYS (IV & SC) arms in the base case of the economic evaluation.	It would be possible to run a sensitivity assuming some proportion of natalizumab-TYS patients received the Biogen funded tests if Biogen provided the proportion of tests received by natalizumab-TYS patients were funded. However, Scenario 3 of the submitted report removed this cost for all natalizumab-TYS patients and found no change to conclusions, so the sensitivity using a proportion would also not find a change in conclusions.
Page 118 (2)	*"However, our clinical advice was that this scheme is*	As above	As above	As above.

Page No. (Paragraph)	Related Text	Company Comment	Resolution	EAG response
	not widely implemented so the cost of JCV testing was included for natalizumab"			
Page 118 (2)	*"Progressive Multifocal Leucoencephalopathy (PML) is an important side effect of some MS drugs, particularly natalizumab and its biosimilar"*	PML also occurs with other MS treatments, as stated in the SmPCs for ocrelizumab, ofatumumab, cladribine, fingolimod, ponesimod and alemtuzumab.	Update the report to provide a more balanced summary of the risk of PML across the relevant therapies within the decision problem.	We extracted all data on the incidence of PML from included studies for all interventions – there were no cases of PML in any included trial
Lack of consideration of Extended Interval Dosing (EID)				
Page 52 (5)	*"Interventions: We restricted inclusion to studies that evaluated the interventions of interest at modes of administration and doses licensed for use in UK unless they were required to create a connected network."*	EID, administering natalizumab-TYS IV or SC Q6W or Q8W instead of SID Q4W is used in clinical practice for some patients (UK clinical opinion).[3,4] Additionally, EID (Q6W) is outlined in the natalizumab-TYS SmPC.[11,12] As described on p15 of the CS, " In clinical practice [13] doses of natalizumab-TYS are administered per patient/year". Rabea et al. (2023) assessed the difference in the efficacy and safety of the EID regimen compared with the SID of natalizumab for patients with MS	Biogen requests that EID is given due consideration in the EAG report, and that the cost savings associated with EID for natalizumab-EID are included in key sensitivity analyses within the economic assessment.	Added "Scenario 9. Sensitivity using EID for natalizumab and natalizumab biosimilar"

Page No. (Paragraph)	Related Text	Company Comment	Resolution	EAG response
		based on a meta-analysis of data identified in an SLR; the study found that EID did not diminish the effectiveness of natalizumab therapy, with a lower risk of clinical relapse and developing newly enlarging T2 hyperintense lesions.[14] These data align with the results from the natalizumab observational program presented at the European Academy of Neurology in 2024; efficacy was similar in patients switching from IV to SC formulation, regardless of SID or EID dosing.[15] Additional benefits of EID are: 1. Cost savings to the NHS (drug costs and HCP time for drug administration). 2. A reduction in natalizumab-TYS exposure during pregnancy. 3. A reduction in the risk of PML. 4. A reduction in travel and in-clinic time for some patients and carers for drug administration. There is little reference to EID throughout the EAG report.		

Page No. (Paragraph)	Related Text	Company Comment	Resolution	EAG response
Page 127 (3)	*"The number of annual doses for Natalizumab are in line with those reported in the Biogen submission"*	This is factually inaccurate as it does not take into account the EID dosing schedule for which evidence was presented in the CS.	To include EID as a key sensitivity analyses and update the report as needed.	Added "Scenario 9. Sensitivity using EID for natalizumab and natalizumab biosimilar"
Drug acquisition costs based on real-world tender pricing				
Table 20, page 124	*"The annual drug acquisition costs are in line with the costs of Natalizumab, Natalizumab bio similar, Ofatumumab and Ocrelizumab reported in the Sandoz submission."* *"The number of annual doses for Natalizumab are in line with those reported in the Biogen submission."*	Biogen is concerned that the drug acquisition cost for natalizumab-TYS is inflated beyond that paid for by the NHS. Natalizumab-TYS is available at a confidential discount provided via national tender agreements that are applicable across all of England. The drug acquisition costs for natalizumab-TYS also do not reflect the use in UK clinical practice of EID, as described in more detail above.	Drug acquisition costs in the base case economic analysis should be updated to reflect those paid by the NHS in routine practice.	These are discussed in the cPAS appendix.
Comparators				
Page 21, 40, 112, 120	*Page 40: "The comparator for this appraisal is*	Biogen is concerned that the comparators included in the appraisal are broader than – and therefore not fully reflective of – those therapies	Removal of inappropriate comparators from the decision problem (IFNs and	The decision problem was set by NICE at the start of the appraisal and, following NICE

Page No. (Paragraph)	Related Text	Company Comment	Resolution	EAG response
	standard care without natalizumab or natalizumab biosimilar. This includes the following interventions: • *Glatiramer acetate* • *Interferon beta 1a* • *Interferon beta 1b* • *Alemtuzumab* • *Cladribine tablets* • *Fingolimod* • *Ocrelizumab.* *The NICE scope suggested that this should only be if alemtuzumab is contraindicated. However, our clinical advisors suggested that this is not reflective of this drug is used in clinical practice and so we will not apply this restriction for our appraisal.* • *Ofatumumab*	used in UK clinical practice. The NHS England treatment algorithm for MS DMTs (shown in Figure 1, page 34 in the EAG report) outlines the relevant treatment options for patients who have received a full and adequate course of at least 1 DMT. These options do not include glatiramer acetate, interferon beta 1a or interferon beta 1b, and these therapies are therefore not considered appropriate comparators for this appraisal. Although these low/moderate efficacy DMTs have been used historically as treatment options for patients with highly active relapsing–remitting multiple sclerosis they are now rarely used in clinical practice due to the current availability of high-efficacy DMTs (UK clinical opinion)[3,4,16] Furthermore none of the recent appraisals in MS included IFNs and GA as comparators in this subgroup (see final scopes) e.g. TA 533, TA 699, TA767. Moreover, as outlined on page 8 of the CS for natalizumab-TYS, fingolimod, alemtuzumab and autologous haematopoietic stem cell transplantation are not considered relevant comparators to natalizumab-TYS.	GA). Base case economic analysis to focus on ocrelizumab, ofatumumab, ponesimod and cladribine.	processes, this was what the EAG worked to.

Page No. (Paragraph)	Related Text	Company Comment	Resolution	EAG response
	• *Ponesimod* • *Autologous haematopoietic stem cell transplantation"*	[redacted][17] Fingolimod use is expected to decline further in the future due to the requirement for CV and skin lesion monitoring (UK clinical opinion).[3,4,16] Autologous haematopoietic stem cell transplantation is used as a last-line therapy when high-efficacy DMT options have been exhausted (UK clinical opinion).[3,4,16] Autologous haematopoietic stem cell transplantation is only available in a small number of NHS centres and very few people with multiple sclerosis are accepted for treatment.[18,19] Alemtuzumab is also considered as last-line therapy for the majority of patients when other DMT options have been exhausted (UK clinical opinion).[4,16] Alemtuzumab is associated with serious adverse events, including thyroid disorders, immune thrombocytopenic purpura and kidney disease.[20]		

Page No. (Paragraph)	Related Text	Company Comment	Resolution	EAG response
Definition of the target population				
Page 31 (2)	*"There is a lack of consensus regarding the definitions for the varying subtypes of disease, with different appraisals and studies using slightly different definitions. "*	Biogen agree that there is a lack of consensus regarding subgroup definitions, and would welcome NICE aligning these definitions. Inconsistency in definitions across technology appraisals brings challenges regarding selecting appropriate evidence on which to base robust decision making.	NICE to confirm definition of appropriate subgroups within RRMS, and then apply to this technology appraisals as appropriate.	We agree that the lack of consensus definition is challenging. We therefore took a broad approach to defined HA RRMS as outlined in the report. This was discussed and agreed with NICE at the start of the appraisal process.
Page 31, Table 2	*"No consensus definition; previous appraisals for NICE have used different definitions. We will use the following broad definition for this appraisal to encompass the variety of different definitions used in existing trials: Unchanged or increased clinical or radiological evidence of disease activity despite treatment with at least one Disease*	Regarding the proposed definition of the target population, Biogen suggest that this should specify at least 12 months of prior DMT to rule out tolerance issues. It may also be helpful, given the differences in definitions in previous appraisals, to include those definitions in this report, for clarity and comparison. Finally, it would be helpful to include that rapidly evolving severe (RES) RRMS comprises a subgroup of patients within highly active RRMS. For example, patients with 2 relapse events within a 12-month period would be considered to meet the criteria for both RES and highly active RRMS.	To update the report as suggested	We have included a clear summary of all definitions of HARRMS used by the included studies. As explained above, we took a pragmatic approach to the definition of this population as outlined in the report and agreed by NICE.

Page No. (Paragraph)	Related Text	Company Comment	Resolution	EAG response
	Modifying Therapy (DMT)"			
Identification of relevant evidence for, and conduct of, network meta-analysis to support decision making				
Page 26 (2)	*"There is no direct evidence on the effectiveness of natalizumab or its biosimilar in patients with highly active disease"*	This statement is only correct based on the restricted criteria for the systematic literature review conducted by the EAG. The CS for natalizumab-TYS includes extensive real-world evidence for the patient population specified in the decision problem, mostly notably from the TOP study. TOP is the largest real-world study of natalizumab-TYS 300 mg IV in patients with RRMS and provides more than 15 years' follow-up for patients which include those with "highly active disease despite a full and adequate course of treatment with ≥1 DMT". Data from TOP was the pivotal efficacy evidence for the extension of the licensed indication for natalizumab-TYS.[21]	Biogen would request that the real-world evidence presented in the CS is given due weight in the decision-making process for this appraisal, consistent with NICE's own framework on incorporating this evidence class in technology appraisals.	Inclusion criteria were set out in protocol and agreed with NICE prior to starting work on the SLR. TOP did not meet inclusion criteria for the review but is referred to in the discussion.
Page 55 (3) Page 79 (3)	*"We therefore expanded our inclusion criteria to include studies that compared ofatumumab to other interventions not specified in our original inclusion*	It is unclear why studies evaluating teriflunomide vs ofatumumab have been included yet studies evaluating teriflunomide vs. placebo have not been utilised to create a fully connected network. There is also a minor typographical error ("lead" should be "led").	Explore including the teriflunomide studies TOWER[22] and TESMO[23] to enable the construction of a fully connected network for NMA. Amend the typographical error.	Studies on teriflunomide and DMF vs. placebo were not included on initial searches because they were out of scope. When it became apparent that teriflunomide would be needed to connect the network, a decision to

Page No. (Paragraph)	Related Text	Company Comment	Resolution	EAG response
	criteria. This lead to the inclusion of an additional 2 studies: ASCLEOPIO I and II[68] that compared ofatumumab to teriflunomide. To create a connected network, we also included the OPTIMUM trial[70] that compared teriflunomide with ponesimod. These three studies are included in our total number of 42 included studies" *"for both outcomes, teriflunomide, ponesimod and ofatumumab did not connect to the network. We were therefore unable to include these interventions in the NMA"*			only include studies comparing teriflunomide against other included interventions was made due to time restrictions. As teriflunomide is not in scope, we were not trying to get data on the effectiveness of this intervention and therefore felt it was reasonable to only include those studies needed to create a connected network. Although the EAG agrees a full network including all licensed DMTs would result in a more robust NMA, we would not expect this to substantially alter the findings of our review or economic model.

Page No. (Paragraph)	Related Text	Company Comment	Resolution	EAG response
				Typographical error has been corrected.
Table 8, page 77	*Outcomes based on the INCOMIN trial*	No commentary, or sensitivity analyses, is provided around the Interferon beta 1b IM 250 study. In general, there is usually high correlation between CDP3 and CDP6 endpoints. However, CDP3 and CDP6 MTC outputs for IFNB-1b are inconsistent (INCOMIN is the only study informing CDP6 for IFNB-1b). The INCOMIN trial, investigating IFNB-1b compared to IFNB-1a, should be excluded from the base case analysis for CDP6 as it is widely considered an outlier by clinical experts. This approach is consistent with the technology appraisals for ocrelizumab (TA533) and ofatumumab (TA699).[24,25]	To remove the INCOMIN study from the analysis	We are aware of INCOMIN (as well as ADVANCE evaluating peginterferon beta 1a) being considered an outlier by some systematic reviews. However, some other recent, well conducted systematic reviews have also included these studies in their analyses too (Gonzalez-Lorenzo M, Ridley B, Minozzi S, Del Giovane C, Peryer G, Piggott T, Foschi M, Filippini G, Tramacere I, Baldin E, Nonino F. Immunomodulators and immunosuppressants for relapsing-remitting multiple sclerosis: a network meta-analysis. Cochrane Database of Systematic Reviews 2024, Issue 1. Art. No.: CD011381; Liu Z, Liao Q, Wen H, Zhang Y. Disease modifying

Page No. (Paragraph)	Related Text	Company Comment	Resolution	EAG response
				therapies in relapsing-remitting multiple sclerosis: A systematic review and network meta-analysis. Autoimmun Rev. 2021;20(6):102826. In our review, effect estimates for annualised relapse rates from these studies were not identified as outliers on model fit graphs assessed by individual study residual deviance (Fig 28), so we did not think excluding these studies from the NMA was appropriate. We agree that there's an inconsistency between CDP3 and CDP6 results for INCOMIN, and a note has been added to highlight this in the text. The initial text also noted that there is considerable uncertainty in the ranking of interventions.

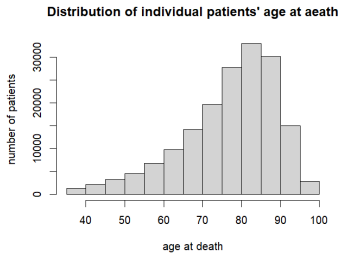
Page No. (Paragraph)	Related Text	Company Comment	Resolution	EAG response
				We have included a sensitivity analysis excluding the INCOMIN trial for the CDP6 outcome. Results were consistent with the primary analysis.
Page 79 (2)	*"Studies reported disease progression at between 6 and 24 months follow-up, with a median of 24 months follow-up. "*	It is unclear if all studies have been included regardless of study duration or if some restriction has been applied. Biogen would recommend the latter. It is also concerning that study durations of 6 months were included, as disability progression requires confirmation 3 or 6 months post-initial assessment and this is unlikely to have been possible for studies of 6 months' duration or less.	To clarify the criteria for selecting included studies and conduct sensitivity analyses restricting study durations e.g. 24 months only.	The inclusion criteria did not restrict studies depending on study duration, however only one study with 6 months of duration was included on CDP3 and CDP6 analyses (ADVANCE) We have added sensitivity analyses including studies with a follow-up of ≥ 24 months for CDP3 and CDP6. positions for the included interventions.
Page 23 (3), Page 67 (1)	*"All studies were considered to be sufficiently similar*	Biogen appreciate the difficulty in aligning patient populations and study designs across studies of	Provide more clarity with regards to the impact of key	Key details of each included trial, including participant

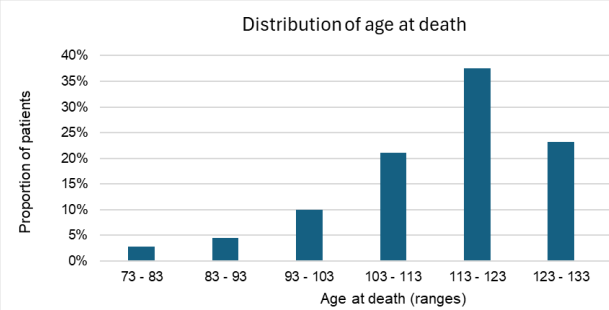
Page No. (Paragraph)	Related Text	Company Comment	Resolution	EAG response
	for inclusion in the NMAs."	RRMS which has been a historical issue in previous and ongoing appraisals. The studies identified by the EAG and incorporated into the NMA include a range of types of MS, different diagnostic criteria of MS, ages of patients, and other factors that are prognostic of progression of disease. Within the studies identified – which themselves include a population broader than that specified in the decision problem – there is sufficient heterogeneity to create uncertainty in the comparative clinical efficacy across the therapies relevant to this appraisal.	differences across the studies included within the NMA on the results. Additionally, add any supporting evidence or validation conducted supporting the assumption that the studies are sufficiently similar for inclusion in the NMA.	and intervention details and differences in how HARRMS and outcomes were defined are clearly summarised in the report. As described in the report, we consider these to be sufficiently similar to include in an NMA.
Page 52 (6)	*"Outcomes: Due to time and resource constraints, we restricted inclusion to studies that reported on at least one of the following outcomes:*	We note that the list of relevant outcomes does not include disease *regression or improvement*. In a recent meta-analysis published by Chappell et al – and included in the CS - there were higher rates of confirmed disability improvement (CDI) for patients receiving natalizumab compared with platform DMT at 24 months and this was significant for 3-month confirmation ($p < 0.0001$).[26] Real-world data from MSBase also highlight improvements in disease outcomes for patients treated with natalizumab.[27,28] Spelman *et al* demonstrated that switching to natalizumab after	To clarify why disease regression was not included in the outcomes	Outcomes were defined at the early stages of the review and were discussed and agreed by NICE. It was not feasible to include all outcomes reported in the trials in our synthesis given tight timelines and resource constraints.

Page No. (Paragraph)	Related Text	Company Comment	Resolution	EAG response
		an inadequate response to first-line therapies (interferon-based therapies, glatiramer acetate, dimethyl fumarate, and teriflunomide) was associated with a significant increase in CDI at 6 months (HR = 1.28; 95% CI 1.01–1.62; *p* = 0.040) compared with switching to fingolimod.[27] Similarly, a Cox regression model based on MSBase data by Butzkueven *et al* showed that patients who initiated natalizumab as first-line therapy had a more favourable time-to-first clinical disease improvement than patients who initiated interferon-based therapies, glatiramer acetate, dimethyl fumarate, or teriflunomide.[28] Together, these data highlight that importance of disease regression or improvement as a relevant clinical outcome that should be included in the EAG's analysis.		
Figure 5, Page 73	*"Figure 5 Forest plot of hazard ratios (HR) and 95% credible intervals for time to CDP3 (fixed effects NMA; RRMS population)"*	The x-axis states "Rate Ratio (RR)" – this should be "Hazard Ratio (HR)". Additionally, for clarity it should be added that the hazard ratios are relative to placebo. There is no explanation provided with regards to the wide confidence intervals for peginterferon beta 1a SC125.	Update x-axis title and add clarification with regards to the reference treatment. Provide narrative explaining the cause of the wide confidence intervals for peginterferon beta 1a SC125.	The figure has been updated. The confidence intervals were taken from the PEGINTEGRIT study, and no explanation is offered in that paper.

Page No. (Paragraph)	Related Text	Company Comment	Resolution	EAG response
Figure 6, Page 74	*"Figure 6 Forest plot of hazard ratios (HR) and 95% credible intervals from fixed effects NMA for time to CDP6 (fixed effects NMA; RRMS population)"*	It is unclear why direct evidence is only depicted for natalizumab IV300, fingolimod O0.5, and cladribine O3.5 when most studies are placebo controlled e.g., peginterferon beta 1a SC125 and interferon betas.	Update the figure to include other direct evidence sources or provide narrative explaining the exclusion of other placebo-controlled studies.	There was an error in the colour depicted in some of the interventions, this has been fixed and updated.
Pages 74–77	Text related to NMAs and related Forrest plots	It would improve clarity and readability to keep the relevant Forrest plots next to the text where the results are discussed	To re-flow the figures so that they are adjacent to the relevant text	The report has been structured in the way that it has to avoid too many changes between portrait and landscape sections. We consider the report easier to read in the way that it is currently structured, but appreciate that others may view this differently
Insufficient information available on the modelling approach				
Section 6	There is insufficient information presented on the modelling assumptions, inputs, and outputs.	There is insufficient information presented on the modelling assumptions, inputs, and outputs. Some examples are provided below. It is the Company's view that all inputs used in the modelling should be presented in the report. This is important for transparency and allows the	All assumptions used in the modelling should be stated and justified in the EAG report.	All inputs are described in Tables 17-26 and 28, the NMA results section, and Appendix 7 on MS Registry analyses.

Page No. (Paragraph)	Related Text	Company Comment	Resolution	EAG response
		validity of assumptions and inputs to be assessed. Furthermore, whilst the London Ontario MS dataset is discussed, it is unclear whether these data inform the base case or any sensitivity analyses. Furthermore, the following outputs should be presented from the economic model such that the external validity of the results can be assessed: • Duration spent in EDSS health states. Based on the R code provided by the EAG, we ran the model for 100 patients across the 17 therapies without making any changes to the shared code. The resulting durations of time spent in EDSS health states appear longer than anticipated for patients with RRMS. • Duration on treatment at each line of therapy. Based on the R code provided by the EAG, we ran the model for 100 patients across the 17 therapies without making any changes to the shared code. The resulting durations on treatment appear longer than anticipated for patients with RRMS. • Undiscounted life years • Undiscounted QALYs	All inputs used in the modelling should be presented in the EAG report. Relevant clinical outputs should be presented in the EAG report such that the validity of the model can be assessed.	We have provided undiscounted costs and QALYs as well as average numbers of key events (i.e., relapse, EDSS increase, EDSS decrease, SAEs) on each treatment. Note that we have also implemented the treatment stopping rule (stopping treatment at EDSS 7.0) suggested below.

Page No. (Paragraph)	Related Text	Company Comment	Resolution	EAG response
Section 6	As described in the row above, there is insufficient information presented on the validity of outputs from the model.	Based on the R code provided by the EAG, we ran the model for 100 patients across the 17 therapies without making any changes to the shared code. The resulting age at death appears significantly higher than expected for patients with RRMS and even exceeds the life expectancy of the UK age- and gender-matched general population (Figure 1). While this observation is derived from our model run, it underscores the importance of presenting model outputs in a way that allows for external validation. Currently, there is insufficient information to assess whether the age at death generated by the EAG model aligns with external data and can be considered valid. **Figure 1: Distribution of age at death across 100 simulations for 17 therapies**	Relevant clinical outputs should be presented in the EAG report such that the validity of the model can be assessed for the base case and key sensitivity analyses.	Thank you for identifying this error, now corrected. The median age at death is 80 (IQR 71-86) min=36, max=100, as shown in the histogram attached.  Note that we have also provided undiscounted costs and QALYs as well as average numbers of key events (i.e., relapse, EDSS increase, EDSS decrease, SAEs) on each treatment.

Page No. (Paragraph)	Related Text	Company Comment	Resolution	EAG response
				
Page 134 (2)	*"The standardized mortality ratio in base case analysis was reported in a case control study of (N=1822) MS patients follow-up up till death (Jick 2014).137 An all-cause mortality Hazard ratio 1.68 (95% CI: 1.38-2.05) compared to the general population was estimated using a proportional hazards cox model"*	Following ongoing discussions as part of the cladribine NICE submission (GID-TA11293), the preference from the EAG in the ongoing appraisal is to apply EDSS-specific SMRs in the base case.[29] Additionally and in relation to the row above, limited information is provided on the clinical outcomes predicted by the model in the sensitivity analysis assuming EDSS-specific SMRs.	The SMR applied to the health states in the base case should align with the latest clinical, EAG, and Committee discussions from relevant NICE appraisals. If an alternative approach is taken, the justification and impact of this should be presented. As above, relevant clinical outputs should be presented in the EAG report such that the validity of the model can	Added "Scenario 13. Sensitivity using EDSS specific mortality" which uses those from Harding et al used in ID6263.

Page No. (Paragraph)	Related Text	Company Comment	Resolution	EAG response
			be assessed for the base case and key sensitivity analyses.	
Page 25 (4) and figure 25, Page 142	*"Validation of EDSS severity over time found less severe trend that was explained by the comparator model mixing RRMS and SPMS patients and not using the latest DMT sequences."*	In Figure 25 a graph is presented titled "*Validation through comparison of EDSS severity over time from economic model (red line with 95% CrI) and predictions from Palace 2014 (purple and green)*". However, it is unclear whether the red line from the EAG economic model reflects the natalizumab arm or, in line with the PALACE data, the interferon beta and glatiramer acetate arms. Note: the code used to re-create this graph was unavailable within the R code shared by the EAG.	Provide clarity on the validation of EDSS severity conducted and the graph presented in Figure 25.	Unfortunately it was infeasible to make the suggested changes in the allotted time.
Page 121 (5)	*Baseline rates of discontinuation due to AEs provided a proxy to waning as in previous appraisals, and were assumed to follow the AFFIRM study for natalizumab and ANTELOPE study for natalizumab biosimilar. For comparators we used the NMA on*	The approach to modelling treatment discontinuation in RRMS has been a key discussion topic in the ongoing NICE appraisal of cladribine (GID-TA11293).[29] At the first Committee meeting it was discussed that a broader definition of discontinuation, beyond only AEs, is relevant. The Committee agreed with this approach in the Draft Guidance Consultation i.e., the Committee believes that treatment switching should be reflected in treatment	The approach and assumptions underpinning the modelling of treatment discontinuation should be compared and validated to the ongoing feedback and discussions in GID-TA11293. Where there are differences in the assumptions, it should be highlighted why this is the case and what impact these	We used NMA on AEs leading to discontinuation whereas in-progress appraisal is using all-cause discontinuation. The latter would lead to greater probability of switching. However, GID-TA11293 is for active, not Highly active population. Also, the treatment is not

Page No. (Paragraph)	Related Text	Company Comment	Resolution	EAG response
	discontinuation due to AEs (Section 5.1.5.) and applied treatment effects to the baseline rates from AFFIRM.	discontinuation rates. Note: the EAG definition of discontinuation in GID-TA11293 is broader still. Additionally, in GID-TA11293 the Committee have suggested using time to next treatment data from CLASSIC-MS to inform the treatment discontinuation for cladribine within the economic evaluation, rather than the CLARITY data.[30]	differences are likely to have on results. The source informing the discontinuation rates for cladribine should be consistent with the ongoing NICE appraisal for cladribine (GID-TA11293).	recommended (appraisal on going) and the model does not allow for treatment switching.
Page 121 (5)	No stopping rule is applied at EDSS 7.	This assumption is inconsistent with UK clinical guidelines, the NHS treatment algorithm, and previously published and ongoing NICE submissions for treatments for MS. The Association of British Neurologists clinical guideline recommends treatment in RRMS to cease once patients are non-ambulatory (i.e. EDSS 7.0).[31] The NHS treatment algorithm states that therapy should be discontinued after the development of inability to walk (EDSS 7.0), persistent for more than 6 months due to MS.[32] Stopping rules are included within the NICE submissions for siponimod (TA656), ponesimod (TA767), ocrelizumab (TA533), alemtuzumab (TA312), and cladribine (TA616 and GID-TA11293).[24,29,33–36]	In line with UK clinical guidelines, the NHS treatment algorithm, and previously published and ongoing NICE submissions for treatments for MS, stopping rules should be applied for treatments from EDSS 7.	After confirming with our independent clinicians that this also applies to highly active RRMS we have included this stopping rule (patients stop treatment after reaching EDSS 7.0) in the base case.

Page No. (Paragraph)	Related Text	Company Comment	Resolution	EAG response
Page 121 (1)	*"The event rates were a combination of natural history (informed by analyses of MS registry data described below) and treatment effects"*	There is limited information available on the data obtained from the MS Registry and the interpretation of these data. E.g., what length of follow-up was available in the MS Registry for each of the therapies? Was the length of follow-up impacted by treatment?	Provide more information on the data obtained from the MS Registry and the interpretation of these data.	Not feasible in the timeline to obtain further estimates from the MS Registry. However, substantial details of the analyses and data were provided in Section 6.8.1 and Appendix 7.
Page 122 (3)	*"The covariate for treatment is only used to obtain baseline rates specific to natalizumab, to which the NMA hazard ratios were applied"*	There is no justification provided as to why the natalizumab data from the MS Registry was used to inform baseline rates.	Provide justification why the natalizumab data from the MS Registry was used to inform baseline rates, and not another treatment. Provide a narrative for the impact of this selection.	The MS Registry analysis is not a randomised, controlled and blinded comparison so should not be used for estimation of relative effects. We there used natalizumab as baseline and applied hazard ratios from the NMA.
Table 19, page 126 Table 24, page 133	*Utility decrements and costs associated with SAEs from AFFIRM*	Biogen is concerned that only SAEs associated with natalizumab-TYS from the AFFIRM trial are included in the model. While we acknowledge that this is a pragmatic approach, and consistent with previous TAs, it does not take into account the known SAEs associated with other therapies. For example, in 2019 the EMA recommended restricting the use of alemtuzumab due to reports	Provide justification for why only natalizumab-TYS SAEs are included in the economic model	In line with prior appraisals and natalizumab the focus of this MTA.

Page No. (Paragraph)	Related Text	Company Comment	Resolution	EAG response
		of rare but serious cardiovascular disorders and immune-related disorders.		
Table 29, Page 141 and Table 8, Page 77	*"The event rates were a combination of natural history (informed by analyses of MS registry data described below) and treatment effects."*	The relative outcomes from the MS Registry presented in Table 29 (page 141) do not align with the mean ranking of interventions from the NMAs presented in Table 8 (page 77). This discrepancy is not discussed within the EAG report.	The validity of outcomes from the MS Registry and the NMA should be discussed. Particularly as these sources provide differing conclusions of relative efficacy. The impact of uncertainties within these data sets on the results should be discussed.	The MS Registry analysis is not a randomised, controlled and blinded comparison so should not be used for estimation of relative effects.
Table 30, Page 141	It is unclear whether the numbers presented in Table 30 are number of people or number of events.	It would be useful for assessing the validity of the MS Registry and the results informing the model to present both the number of people and the number of events. Additionally, there is no narrative on the potential impact of low patient numbers or events on the analysis.	Further detail and reporting should be provided on the MS Registry including data cuts, cleaning processes (if applicable), inclusion/ exclusion criteria, sample sizes per treatment and follow-up over key timepoints. Clarify whether the numbers presented in table 30 are number of people or number of events and add the missing variable.	Numbers of people (sample size) were provided in Section 6.8.1 and Appendix 7. There is considerable discussion of the impact of low sample sizes.

Page No. (Paragraph)	Related Text	Company Comment	Resolution	EAG response
			Provide narrative on the potential impact of low patient numbers or events on the analysis – particularly in relation to the relative outcomes differing from those estimated by the NMA.	
Page 117 (5) and Figure 24, Page 120	*Treatment status is a key attribute, and the sequence of treatment is represented in Figure 24*	The available therapies at 2nd, 3rd, and 4th line are presented in Figure 24. However, the text does not explain whether 3rd line and 4th line therapies are modelled as a weighted basket of available treatments or whether subsequent therapies are sampled from the available therapies (and how this sampling is conducted e.g., random sampling with replacement). This information is available within the R-based model. However, it is the Company's view that the assumptions and inputs underpinning the model should be presented in the EAG report.	All assumptions used in the modelling should be stated and justified in the EAG report. All inputs used in the modelling should be presented in the EAG report.	Added a footnote under Figure 24: *Patients modelled on individual therapies from options at 3rd and 4th line, rather than a basket.
Page 117 (5)	*"patients can progress to SPMS on any line of RRMS therapy and are then assumed to receive an average*	In the report, it is unclear whether there are different risks of progression to SPMS depending on the line of therapy. This information is available within the R-based model. However, it is the Company's view that the assumptions and	All assumptions used in the modelling should be stated and justified in the EAG report.	This had been stated in the report but is now also included in Table 28 on the base case assumptions: "No effect assumed by RRMS

Page No. (Paragraph)	Related Text	Company Comment	Resolution	EAG response
	'basket' of approved therapies"	inputs underpinning the model should be presented in the EAG report.	All inputs used in the modelling should be presented in the EAG report.	treatment on event rates after progression to SPMS"
Page 22 (3)	*"Patients who progressed SPMS could experience the events EDSS increase, relapse, SAEs, and death"*	In the report, it is unclear whether EDSS regression is included in the SPMS health state. This is excluded on Page 22 and included on Page 121. This information is available within the R-based model. However, it is the Company's view that the assumptions and inputs underpinning the model should be presented in the EAG report.	All assumptions used in the modelling should be stated and justified in the EAG report. All inputs used in the modelling should be presented in the EAG report.	EDSS regression is excluded, in line with the model diagram in Figure 24. The confusion arose as we requested this event rate from the MS Registry to confirm our assumption. We've therefore added the following footnote below Table 15: *Not used in model, only for exploration
Page 121 (3)	*"Relapse rates in SPMS were informed by the MS registry analyses and included regression on EDSS severity"*			
Table 25, Page 135	For treatment effects, Table 25 references the NMA Section 5.1.2 – 5.1.5.	It is unclear what assumptions are made where no relative efficacy data are available from the NMAs. This information is available within the R-based model e.g. ofatumumab is assumed equivalent to ocrelizumab for CDP outcomes. It is the Company's view that the assumptions and inputs underpinning the model should be presented in the EAG report.	All assumptions used in the modelling should be stated and justified in the EAG report. A fully connected network could be generated by including studies for teriflunomide as previously commented.	Table 28 of the report was updated with treatment class relative effects assumptions stated. Also added a sentence "Treatment class effects was assumed where relative treatment effects not estimated by NMA." in

Page No. (Paragraph)	Related Text	Company Comment	Resolution	EAG response
				Methods Cost-effectiveness on P. 22 and in 6.5.1 clinical outcomes and treatment effects on P.126.
Table 19, Page 126	The utility decrement and duration for PML is assumed to be -0.30 and 365.25, respectively.	It is unclear how these values were selected; the utility decrement and duration for PML differs across the appraisals cited in Table 19. E.g., TA616 and TA312 use -0.2 and apply this only over 93.1 days.	Provide justification why the values from TA767 and TA699 were used rather than TA616 and TA312.	The values chosen were accepted in recent Technology appraisals.
Table 20, Page 126-127	Table 20 reports the proportion of patients treated each year.	It is unclear where these data are sourced from and how it is applied within the modelling. This information is available within the R-based model. However, it is the Company's view that the assumptions and inputs underpinning the model should be presented in the EAG report.	All assumptions used in the modelling should be stated and justified in the EAG report.	The values relate to the proportions of patients treated (100%) in years 1 and 2 and re-treated years 3, 4, 5+ depending on treatment as advised by clinicians.
Table 20, Page 126-127	Hawton et al is referenced for relapse costs.	There is no detail on the relapse costs used in the model. This information is available within the R-based model. However, it is the Company's view that the assumptions and inputs underpinning the model should be presented in the EAG report.	All assumptions used in the modelling should be stated and justified in the EAG report. All inputs used in the modelling should be presented in the EAG report.	The costs and description have been added to the report and model inputs updated in table 25.
Table 21, page 128	Table 21 reports the annual treatment administration costs	It should be acknowledged that whilst the infusion-based therapies (natalizumab, ocrelizumab and alemtuzumab) have all been assigned the same unit cost for infusion, there is	EAG to amend report to acknowledge differences in infusion and observation times.	Unfortunately, the HRG cost codes do not allow for this level of detail, they are counted as visits.

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		a significant difference between the therapies for both infusion and observation times. • Natalizumab-TYS IV: infusion over approximately 1 hour and patients to be observed for 1 hour after the completion of the infusion. Patients should be observed for the first 12 doses, after which the observation period maybe removed or reduced should no infusion reactions be experienced. Total time: 1-2 hours[11] • Ocrelizumab: infusion over approximately 3.5 hours followed by observation for at least 1 hour after the completion of the infusion. Should a patient not experience a serious infusion-related reaction to any infusion, a shorter 2-hour infusion can be used for subsequent doses. Pre-medications are required prior to each infusion for a duration of 30-60 mins.[37] Total time – 3.5-5.5 hours • Alemtuzumab: infusion over a period of approximately 4 hours. Observation for infusion reactions is recommended for a minimum of 2 hours after infusion. Pre-medications are required immediately prior to the first three infusions in each cycle.[20] Total time: 6 hours		

Page No. (Paragraph)	Related Text	Company Comment	Resolution	EAG response
Table 24, Page 133-134	The cost of PML is assumed to be £14,333.02.	It is unclear how this value was selected the cost for PML differs across the appraisals cited in Table 19. E.g., TA616 used £1,268.11 and TA699 used £1,077.72.	Provide justification why the value assumed is valid, rather than the values from other published appraisals.	Kindly note the Annual Management costs mentioned for PML are inaccurate in the case of TA699 where £13,258.28 is the correct amount costed. In the case of TA616 the costing information is unclear although the total cost is £1268.11, the unit cost is £4503.35 for a single plasma exchange and resource use quotes study where 80% of patients receives 3 plasma transfusions. In addition to the appraisals brought to our attention, TA767 costed £19,391.18.
Table 25, Page 134-135	There are serious adverse events listed in Table 25 for which no utility or cost data are presented.	It is unclear what impact these serious adverse events have in the model. This information is available within the R-based model. However, it is the Company's view that the assumptions and inputs underpinning the model should be presented in the EAG report.	All assumptions used in the modelling should be stated and justified in the EAG report.	Updated table 25 to reflect costs were not modelled for: falls, convulsion, cervical dysplasia, alcohol poisoning, head injury and thermal burn. Disutilities were not modelled for: cholelithiasis, rehabilitation therapy, falls, convulsion, gastritis, cervical dysplasia, alcohol poisoning,

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				head injury and thermal burn.
Factual Accuracies in the R-based Model				
Page 126-127, Table 20	In the R-based model, the annual cost of fingolimod is £19,176	In Table 20 (Page 126-127), the annual cost of fingolimod is £19,169.	Clarify the correct number and update throughout.	Updated the report.
Page 124, Table 16	In the R-based model, the disutility of relapse SD is 0.013.	In Table 16 (Page 124), the disutility of relapse SD is 0.016.	Clarify the correct number and update throughout.	Updated the model.
Remaining Factual Accuracies in the EAG Report				
Page 10 – 14	*"List of Tables"*	The page numbers do not correspond to the position of tables throughout the document.	Update the list of tables.	We did run an update to all cross-references and indexes as a last step before submitting the report. We have done this again and have checked to make sure this is now correct.
Page 31 (1)	*"To provide an accurate and reliable evaluation of confirmed disability progression (CDP), two consecutive*	This statement should also mention the potential for an evaluation of CDP at 3 months, and commentary around a positive 3-month assessment being more likely to be influenced by a recent relapse i.e. a positive 3-month CDP may not be as indicative of permanent disability progression as a CDP conducted at 6 months.	Update the text to include a 3-month CDP	We have edited this as follows "To provide an accurate and reliable evaluation of confirmed disability progression (CDP) at 3 and 6 months, two consecutive

Page No. (Paragraph)	Related Text	Company Comment	Resolution	EAG response
	examinations should be carried out by the same physician at least 6 months apart."			examinations should be carried out by the same physician at least 3 and 6 months apart"
Page 54 (1)	*"This restricted NMA in the general RRMA population was plotted together with results from the equivalent network in the HARRM population for comparison"*	RRMA and HARRM should be RRMS and HARRMS, respectively	To correct typographical errors	This has been corrected
Table 7, page 62	*Risk of bias table*	Row that includes the CONFIDENCE study. Cell marked "High" is highlighted the incorrect colour. There is also inconsistency in the shade of orange used to highlight "High" throughout the table	To amend incorrect table shading	This has been corrected
Page 71 (1)	*"followed by natalizumab (2.2, 95 % CrI 1, 4; 17%)"*	Mean ranking for natalizumab IV300 is reported as (2.2, 95% Crl 1,4) for ARR on Page 71. In Table 8 (Page 77), this is (2.3, 95% Crl 1, 4).	Clarify which is correct and update the incorrect number.	This has been corrected – it should have been 2.3, 95% Crl 1, 4.
Page 71 (1)	*"There was greater uncertainty for natalizumab biosimilar which had a 4% probability of ranking first"*	Probability of ranking first for natalizumab biosimilar is reported as 4% for ARR on page 41. In Table 8 (Page 77), this is 5%.	Clarify which is correct and update the incorrect number.	This has been corrected – it should have been 5%
Page 71 (1)	*"This shows that the RR (95% CrI) for natalizumab*	This does not align with the NMA results presented in Table 60 (Page 317; 0.65 (0.34, 1.26)). The 0.65 (0.33, 1.23) comes from the	Clarify whether the study results or the NMA results	This has been corrected – it should be the NMA results

Page No. (Paragraph)	Related Text	Company Comment	Resolution	EAG response
	compared to natalizumab biosimilar, the key comparison for this appraisal, was 0.65 (0.33, 1.23), suggesting no difference between the ARR for these two interventions."	natalizumab vs. natalizumab biosimilar study reported in Table 10 (Page 95). However, Page 71 references the NMA in the text.	should be presented on Page 71 and clarify and/or update.	
Page 80 (2)	*"Figure 5 shows the HR and 95% credible intervals (CrI) for comparison of each intervention included in the network with placebo under the selected random effects model"*	Figure 5 (Page 73) states the HR and 95% credible intervals (Crl) for the fixed effects model – not the random effects model.	Clarify which is correct and update the incorrect text.	This should be fixed effects and has been corrected
Page 81 (2)	*"Figure 6 shows the HR and 95% credible intervals (CrI) for comparison of each intervention included in the network with placebo under the selected random effects model"*	Figure 6 (Page 74) states the HR and 95% credible intervals (Crl) for the fixed effects model – not the random effects model.	Clarify which is correct and update the incorrect text.	This should be fixed effects and has been corrected

Page No. (Paragraph)	Related Text	Company Comment	Resolution	EAG response
Page 83 (2)	*"Ocrelizumab had the highest mean ranking (1.4, 95 % CrI 1, 3) and the greatest probability of ranking first (68%)"*	Table 8 (Page 77) states ocrelizumab has a 0% probability of ranking first for the MRI Gd+ outcome.	Clarify which is correct and update the incorrect text.	The text is correct – the numbers in table 8 have been corrected.
Page 83 (2)	*"All other interventions had a 0% probability of ranking first"*	Table 8 (Page 77) states that alemtuzumab has a 68% probability of ranking first.	Clarify which is correct and update the incorrect text.	The text is correct – the numbers in table 8 have been corrected. The probabilities of ranking first in table 8 had been switched for alemtuzumab and ocrelizumab
Page 84 (3)	*"The DIC (26.4 vs 27.9) and residual deviance (14.5 vs 15.6 on 18 data points) were very similar for both fixed and random effects models"*	In Table 76 (Page 338) the residual deviance is 15.4 vs 15.6.	Clarify which is correct and update the incorrect number.	This was a typo and has been corrected
Page 85 (1)	*"Figure 7 shows the hazard ratio (HR) and 95% credible intervals (CrI) for comparison of each intervention included in the*	This paragraph is specific to the time to developing at least one new or enlarging T2 weighted MRI lesions endpoint – with results shown in Figure 8 (Page 76; not Figure 7).	Clarify which is correct and update the incorrect reference.	This has been corrected

Page No. (Paragraph)	Related Text	Company Comment	Resolution	EAG response
	network with placebo"			
Page 85 (1)	*"All interventions except interferon beta 1a SC44 were associated with a greater reduction (i.e., HR<1 AND 95% CrI excluding 1.00) in the risk of relapses compared to placebo"*	This paragraph is specific to the time to developing at least one new or enlarging T2 weighted MRI lesions endpoint. This conclusion does not align with the relevant endpoint.	Clarify and update the text.	This has been corrected to "All interventions except interferon beta 1a SC44 were associated with a greater reduction (i.e., HR<1 AND 95% CrI excluding 1.00) fewer patients with new or enhancing T2 lesions compared to placebo"
Page 85 (1)	*"All other interventions had a 0% probability of ranking first"*	In Table 8 (Page 77), alemtuzumab has a 3% probability of ranking first for the relevant time to developing at least one new or enlarging T2 weighted MRI lesions endpoint.	Clarify and update the text.	This has been corrected: Ocrelizumab had the highest mean ranking (2.2, 95 % CrI 1, 5) and a similar probability of ranking first (30%) to natalizumab biosimilar (3.0, 95 % CrI 1, 7; 31%) and interferon beta 1b (3.1, 95% CrI 1, 8; 32%). Natalizumab had the next highest ranking (3.5, 95% CrI 1, 6) and a 4% probability of ranking first, followed by cladribine (4.2, 95% CrI 1, 7; 3%).

Page No. (Paragraph)	Related Text	Company Comment	Resolution	EAG response
Page 3 (5), Page 24 (2), and Page 87 (2)	*"any AEs (HR 1.06 (0.77, 1.46)", "There was no evidence of a difference between natalizumab and natalizumab biosimilar 1.06 (0.77, 1.46) in the risk of any AEs", and "This shows that the HR (95% CrI) for natalizumab compared to natalizumab biosimilar, the key comparison for this appraisal, was 1.06 (0.77, 1.46) suggesting no difference between the HR for these two interventions"*	Table 80 (Page 344) reports this hazard ratio as 1.06 (0.79, 1.45).	Clarify which is correct and update the incorrect number(s).	This has been corrected -the number in the table was correct *1.06 (0.77, 1.46)* is from the RE analysis)
Page 90 (2)	*"Results were very similar for both random and fixed effects models (Table 82in Appendix 5)"*	This text is specific to the discontinuation due to AEs endpoint – with results shown in Table 85 (page 350). Not Table 82.	Clarify and update the reference.	This has been corrected to Table 85

Page No. (Paragraph)	Related Text	Company Comment	Resolution	EAG response
Table 10, Page 95	*"Data on Natalizumab and Natalizumab biosimilar" column*	The source of data in this column is unclear. CP3, CP6, and MRI hazard ratios align with the results from the NMA tables in the Appendices. However, the hazard ratios presented for ARR, any AEs, and treatment related AEs do not align with the NMA. • ARR reported as 0.65 (0.34 – 1.26) from the NMA. • AEs reported as 1.06 (0.79 – 1.45) from the NMA. • Treatment related AEs, an NMA was not conducted.	Clarify the source of data in Table 10 and either add references or update in line with the NMA results.	We have clarified this by adding "from NMA" or from ANTELOPE study.
Page 98 (3)	*"The heterogeneity standard deviation estimated by the random effects model (tau (95% CrI) of 1.40 (0.05, 3.95) in Table 59) was high when compared to the average treatment effect on the log rate ratio scale (-0.58 in Table 59)"*	This text is specific to the ARR endpoint in the HARRMS population. Table 59 (Page 315) shows the results of the RRMS population and the numbers do not align with the text. Table 88 (Page 354) shows the relevant numbers from the text for the ARR endpoint in the HARRMS population.	Clarify and update references.	This has been corrected to Table 88.
Table 19, Page 126	The utility decrement of -0.07 and duration (days) of 24.5 for gastritis	In the publicly available documents from TA616, these numbers could not be matched. 24.5% was reported as the probability of the event.	Clarify source of the inputs for gastritis and any assumptions required.	Corrected the report and model has been updated by setting the disutility for gastritis to zero.

Page No. (Paragraph)	Related Text	Company Comment	Resolution	EAG response
	are referenced from TA616.			
Table 4 (Page 42-43), Table 20 (Page 126-127), and Table 21 (Page 128-129)	The dosing information presented across these tables is inconsistent.	The dosing information presented across these tables is inconsistent. • In Table 4 (Page 42-43) ofatumumab states 20mg every 4-weeks as an SC. However, Table 20 (Page 126-127) states 50mg 15 times a year. • In Table 4 (Page 42-43) alemtuzumab states 12mg for 5-days in month 1, then 3-days in month 12. In Table 20 (Page 126-127) and Table 21 (Page 128-129) this states five in the first year, then three in the following year. • In Table 21 (Page 128-129), unclear why some oral therapies have costs and others do not e.g., ponesimod, cladribine, and fingolimod.	Clarify which dosing schedule is correct and ensure consistent throughout report and model.	Table 20 in the report updated the dosage to 20mg. The assumption for 15 doses in year 1 comes from the ERG's report on TA699. No Costs or redacted cost assumptions in table 21 are based on previous appraisals and referenced.
Table 4 (Page 42-43), Table 20 (Page 126-127), and Table 21 (Page 128-129)	Alemtuzumab re-treatment is not included within the economic evaluation.	In addition to the discrepancies between Table 4 (Page 42-43), Table 20 (Page 126-127) and Table 21 (Page 128-129) for alemtuzumab administration (see row above), the economic evaluation does not include rates of alemtuzumab re-treatment. Alemtuzumab re-treatment is relevant to UK clinical practice and rates were implemented in the base case in the NICE submissions for alemtuzumab (TA312) and for the alemtuzumab comparator in the ocrelizumab appraisal (TA533).[24,33] In these	In line with UK clinical practice and previous NICE appraisals, alemtuzumab re-treatment should be included in the base case.	Table 20 in the report details the proportions of patients treated (100%) in years 1 and 2 and proportions re-treated years 3, 4, 5+ depending on treatment as advised by clinicians.

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		appraisals, the rates of re-treatment were informed by the CARE-MS I, CARE-MS II and CAMMS233 clinical data.[38–40] In both NICE appraisals, clinical experts confirmed the use of alemtuzumab re-treatment for some patients in UK clinical practice.		
Page 127, Table 20	A row is included for natalizumab SC biosimilar.	The SC form of the natalizumab biosimilar does not exist.	Remove row and mention of the natalizumab SC biosimilar throughout.	Thanks for spotting, removed.
Page 129 (3) Page 135 (1)	"Patients progressing on to SPMS are treated with Peginterferon beta 1a or Siponimod." "Patients who discontinue treatment are allowed to switch onto one of the higher line treatments. Patients who progress on to SPMS are assumed to be treated with Siponimod or Peginterferon beta 1a for the remainder	Factually inaccurate in both sections, “Peginterferon beta 1a” should be replaced with “beta-interferon”. Peginterferon beta 1a does not have marketing authorisation to treat SPMS.	Amended text as suggested	Changed in both cases.

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	of their time in the model."			
Page 133 (1)	*"The costs have been inflated to 2022/2023 prices using the NHSCII pay and prices index, details provided in Table 23"*	On Page 126 (Paragraph 2), it states all costs inflated to 2023/24.	Clarify the correct cost year and update throughout.	Corrected to 2022/2023
Page 134, Table 25	The estimate reference reported for the initial EDSS distribution is Table 26.	The EDSS initial distribution is presented in Table 28 – not Table 26.	Clarify and update references.	Corrected
Page 135, Table 25	The estimate reported for the standardised mortality ratio is: "HR 1.68 (95%CI: 2.05-1.38)"	This should be 1.68 (1.38 – 2.05).	Update the text.	Corrected
Page 135, Table 25:	The estimates reported for the SMR by EDSS are 1.6, 1.84, and 4.4.	In Pokorski et al. these values are 1.6, 1.84, and 4.44.	Clarify whether 4.4 or 4.44 was used in the modelling. If 4.4 was used, update using the 4.44 in the document and model as per the publication.	Corrected in model but had been incorrect in report. Updated 4.44 in the report
Page 138, Table 27	"Uses HA RRMS from MS Registry for baseline rates, all	The model uses data from all RRMS for EDSS regression baseline rates.	Clarify and update text.	Thank you for spotting this error. We have changed to say " Uses HA RRMS from MS

Page No. (Paragraph)	Related Text	Company Comment	Resolution	EAG response
	RRMS fixed effects from NMA for treatment effects, EDSS starting distribution from MS Registry for HA RRMS"			Registry for baseline rates on EDSS increase, progression to SPMS and time to relapse for HA RRMS patients. Uses all RRMS from MS Registry for EDSS decrease for HA RRMS patients. Uses all SPMS for EDSS increase and time to relapse for SPMS patients."

NICE National Institute for Health and Care Excellence

Abnag Comments

Page No. (Paragraph)	Company Comment	Resolution	EAG response
Full report	Whilst natalizumab is not the most cost effective in the analysis, there was no difference in QALYs with 95% CI completely overlapping. If natalizumab is equivalent to any other DMT in terms of cost effectiveness then we should be able to offer patients this choice, as on efficacy in the NMA it consistently ranks within the top 2 across a range of measures.	Further, six-weekly natalizumab dosing is now widespread across the NHS, which reduces cost over the course of a calendar year (average 13.5 doses with 4 weekly administration vs 9 doses with extended interval dosing) alongside mitigating some of the PML risk and costs associated with this rare complication.	We have added "Scenario 9. Sensitivity using EID for natalizumab and natalizumab biosimilar"
Full report	The cost of John Cunningham human polyomavirus (JCV) testing was included for both natalizumab and natalizumab biosimilar as clinical advice was that the manufacturer scheme of paying for JCV testing is not widely available. We would argue that this assumption is flawed	At present, we only use the manufacturer scheme – there is no NHS test that has demonstrated equivalence of results that allows us to risk stratify in a way that guides clinical practice in terms of monitoring and risk mitigation.	Followed independent clinical advice.
Full report	This report by definition is purely based on cost effectiveness and does not consider equalities issues related to protected characteristics. Natalizumab has a well-established safety profile in pregnancy and denying women with highly active MS the opportunity to switch onto this therapy means that those with breakthrough disease or adverse events on first line therapy such as ocrelizumab are forced to switch to a therapy of lower efficacy given the teratogenic considerations around other treatments.		This can be discussed by the committee but is beyond scope of EAG report.

NICE National Institute for Health and Care Excellence

Novartis Comments

Page No. (Paragraph)	Company Comment	EAG response
Page 128, Paragraph 2	Statement that patients do not see differences between SC and IV intensity of resource is misleading as patients would only require 1 x NHS resource utilisation in initiation & ongoing administration of Ofatumumab. Expansion of the nurse time required to deliver the first dose observation of Ofatumumab is not highlighted and differentiated from Beta Interferons.	We followed independent clinical advice and rechecked that they agreed with our base case assumption. However, we explored this in "Scenario 5. Sensitivity assuming a reduction in Natalizumab-SC administration costs" and found no impact on conclusions.
Page 128, Table 21	Annual treatment costs are misleading and overstated – Year 1 and Year 2 onwards state 3 hours of Nurse time (Band 7). NHS resource utilisation, as defined within the Ofatumumab SmPC, requires nurse observation in relation only to the first dose of the initiation and does not require nurse time in Year 2 or beyond.	Thank you for pointing this out, we agree and corrected the report and model to require no nursing time years 2 onwards.

NICE National Institute for Health and Care Excellence

Sandos Comments

Page No. (Paragraph)	Company Comment	EAG response
Full report	Issue 1: Comparator treatments likely to be displaced if natalizumab reimbursement extended to HA RRMS • Natalizumab is a monoclonal antibody DMT classed as a drug of high efficacy (average relapse reduction substantially more than 50%) as per ABN guidelines. Natalizumab would therefore be used in patients for whom a high efficacy biologic treatment is considered the most appropriate treatment approach on the balance of benefit–risk in the context of the patient need. This is reflected in ABN guidelines, which state that "alemtuzumab and natalizumab are appropriate where individuals and their multiple sclerosis specialist neurologists are most concerned to achieve high efficacy, despite the more complex safety profile compared to Category 1 drugs". • Alternative licensed high-efficacy biologic treatments other than natalizumab are ocrelizumab and ofatumumab (both licensed after the 2015 ABN guidelines were published) and alemtuzumab; therefore, these represent the treatment options that would represent the most relevant treatment choice alternatives to natalizumab in clinical practice. However, alemtuzumab is associated with a specific and complex safety profile that has restricted its use in UK clinical practice, and Sandoz understands that alemtuzumab has limited usage in practice as a treatment option among patients with 'highly active' RRMS. As such, ofatumumab and ocrelizumab represent the most relevant comparators to natalizumab for patients with highly active disease after at least one DMT. • The other comparator treatments considered in the AG analysis are not relevant comparators in clinical practice as they are not 'high efficacy' biologic treatments and would therefore generally be used in a different patient-specific clinical context to natalizumab. Sandoz further note that the NHS England treatment algorithm for DMTs does not list older DMTs such as GA and the IFNs as escalation options following disease activity on first- or second-line treatment, as such the broad NICE scope for this appraisal	No response from EAG needed

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	is misaligned with NHS clinical practice. • Whilst Sandoz acknowledge the need for the AG to address the full NICE scope for the purposes of following NICE process, they are disappointed that the interpretation and conclusions have not focussed on the realistic clinical comparison to similarly efficacious DMTs. • Sandoz request that NICE direct the AG to present scenario analyses to the Appraisal Committee Meeting covering (a) the limited comparator list proposed by Sandoz using the AG model; (b) the limited comparator list proposed by Sandoz using the cost comparison methodology proposed by Sandoz in their submission to this appraisal; (c) the limited comparison list included in the NHS England treatment algorithm for escalation following activity on first- and second-line DMTs, using the AG model. Sandoz anticipate that these analyses will demonstrate a material impact on the cost-effectiveness estimates.	
	Issue 2: Drug prices used in the economic analysis • While the AG report mentions the existence of confidential discounts for both interventions and most comparators initially, it then omits to remind the reader of this in all subsequent analyses, and has produced a Report that draws conclusions from an economic analysis that has knowingly been conducted on prices which are not relevant (i.e. list prices). These conclusions may therefore easily mislead the reader. • Whilst Sandoz strongly appreciate the necessity for commercial confidentiality of the prices themselves, they request that explicit mention of the analyses at true prices be added to the report and conclusions drawn to the extent that is compatible with maintaining confidentiality; at a minimum the reader must be clearly reminded that the true conclusions on cost-effectiveness will be drawn from confidential prices only and not from the presented EAG analysis. Sandoz note that such conclusions are routine in NICE STA appraisals to allow public understanding of the appraisal process. • Additionally, Sandoz note that the price of their product has recently been updated following NHS England's latest pricing review of natalizumab biosimilar and request that this most up to date price be included in the analyses	cPAS results restricted to the confidential appendix.

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	presented to the Appraisal Committee Meeting. Sandoz anticipate that these analyses will demonstrate a material impact on the cost-effectiveness estimates.	
	Issue 3: Omission of extended interval dosing • Sandoz note that the SmPC for each natalizumab product provides the option for "extended interval dosing", whereby patients receive six-weekly administrations of natalizumab rather than the standard four-weekly dose. Sandoz request that the AG produce economic analyses that consider some proportion of patients to follow this regimen. • As laid out in the submission by Sandoz to this appraisal, based on clinical opinion sought by Sandoz, in one centre in the UK approximately 25% of patients received EID dosing. The SPC for natalizumab notes that "in anti-JCV antibody positive patients, extended interval dosing of natalizumab (average dosing interval of approximately 6 weeks) is suggested to be associated with a lower PML risk compared to approved dosing." • The issue of extended interval dosing is likely to have a material impact on the cost-effectiveness estimates and Sandoz request that this issue is discussed in full at the Appraisal Committee Meeting, and therefore request that NICE ensure that the AG are directed to produce meaningful economic analyses on this point prior to the Appraisal Committee Meeting.	Added "Scenario 9. Sensitivity using EID for natalizumab and natalizumab biosimilar"
	Issue 4: Cost of intravenous administration • Sandoz note that the cost quoted by the AG for intravenous administration, is materially higher than that used by the NICE budget impact test even though both use currency code AA30F; given the importance of administration cost as a driver of the overall cost of natalizumab, Sandoz request that NICE direct the AG to align to the BIT cost used, as accepted by NICE and NHS England.	NICE confirmed that the budget impact test should align with the MTA, not the other way around.
	Issue 5: AG inappropriately model natalizumab biosimilar as a clinically separate product to the originator • Sandoz are concerned that the AG Report treats the natalizumab biosimilar product as a	Added "Scenario 8. Sensitivity assuming clinical equivalence for natalizumab and

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	separate clinical product to the originator product, rather than assuming the biosimilar differs only in price. Any clinical data are inherently from small studies focussed on meeting the needs of the biosimilar regulatory process, putting a biosimilar at a disadvantage if it is treated as a separate clinical product in an appraisal. • Given the NICE position statement on biosimilars, wherein any approval for an originator product automatically applies to all future biosimilars, Sandoz request that NICE direct the AG to treat biosimilar natalizumab as differing only in price. As such Sandoz request that the AG report be amended to remove all interpretations and conclusions and other statements which are predicated on assuming a clinical difference between originator and biosimilar. In addition, all economic analysis must be amended such that the biosimilar differs from the originator only with respect to costs.	natalizumab biosimilar"
	Issue 6: Company submissions and cost comparison methodology • Sandoz made a submission in good faith. We believe we have a reasonable expectation that our submission will be given due consideration by the AG. This appears not to be the case. This reduces our confidence that the consultation process adequately responds to consultee views. The risk is that the committee publishes guidance based on incomplete information. We urge NICE and the AG to reconsider the company submissions.	We apologise that it was necessary to prioritise relevant evidence. If the company had submitted analyses aligned with the NICE decision problem it would have been given greater consideration.
	Issue 7: AG NMA connectivity in the main RRMS analyses • Sandoz note that defects in the AG NMA resulted in one of the key high efficacy DMTs, ofatumumab, being disconnected in some analyses, and minimally connected in others. • Sandoz, in their submission to this appraisal, provided citation to a recent high quality NMA of DMTs which shows that a properly connected network of all DMTs, including ofatumumab, can be undertaken with the inclusion of all licenced DMTs. Sandoz note that the AG have correctly included teriflunomide in their network, even though it is not within the scope for this appraisal, because it is a comparator in the ofatumumab trials. Sandoz note that if the AG had taken care to include all DMT trials in their main RRMS network, including those for teriflunomide and DMF, their NMA would become better	Studies on teriflunomide and DMF vs. placebo were not included on initial searches because they were out of scope. When it became apparent that teriflunomide would be needed to connect the network, a decision to only include studies comparing teriflunomide against other included interventions was made due to time restrictions.

Page No. (Paragraph)	Company Comment	EAG response
	connected and more robust. • Rather than spend time updating the AG NMA, Sandoz request that the published NMA cited in their submission be presented to the Appraisal Committee Meeting as an alternative and more appropriate source of relative effectiveness estimates.	As teriflunomide is not in scope, we were not trying to get data on the effectiveness of this intervention and therefore felt it was reasonable to only include those studies needed to create a connected network. Although the EAG agrees a full network including all licensed DMTs would result in a more robust NMA, we would not expect this to substantially alter the findings of our review or economic model.
	Issue 8: AG mortality assumptions in the economic analysis • Mortality in RRMS relative to the general population is well recognised to increase at more severe stages of the disease, however the AG have implausibly modelled that the relative risk of death is equal from EDSS 1 to EDSS 9. • Sandoz recognise the criticisms of the most commonly used source of mortality inputs for prior appraisals but would contend that assuming an equal risk across disease severity is more implausible than applying outdated risks. • Sandoz would note that a relatively recent analysis of a UK cohort is available in the literature, which again finds that mortality risk increases with EDSS: o Harding, Katharine et al. A contemporary study of mortality in the multiple sclerosis population of southeast Wales. Multiple Sclerosis and Related Disorders, Volume 25, 186 - 191 • Given the results of the AG scenario analyses, it appears that this assumption may demonstrate a material impact on the cost-effectiveness estimates.	We have added "Scenario 13. Sensitivity using EDSS specific mortality" which used the Harding SMRs used in ID6263.

Page No. (Paragraph)	Company Comment	EAG response
	Issue 9: Cost of serious adverse events in the AG model • The values of many of the inputs in Table 24 of the AG Report appear to lack face validity, including £7k for a urinary tract infection, £21.5k for 52 face-to-face consultant appointments for depression, and the use of lower respiratory tract infection costs for anaphylaxis. • Sandoz requests that all inputs in Table 24 are reconsidered for face validity.	Thank you for pointing this out. We updated the assumptions in the report (table 24)and model, summarised as follows: Assumed a lower severity by taking the midpoint (CC 6-8) for the urinary tract Infections hospital stay. Reduced the number of appointments to 32, calculated as mid-point between 12 (non-severe depression) and 52 (severe depression) appointments assumed in TA533. Assumed clinical immunology and allergy service visits and an allergic reaction day case for treating anaphylactic reaction. Assumed an allergic reaction day case for treating hypersensitivity reaction.
	Issue 10: Cost of JCV testing H• Sandoz provide a JCV testing service for the NHS and can confirm that a large number of tests (more than [redacted] to date) have been provided under this service; Sandoz are not aware of any difficulties in the NHS accessing their funded testing service. • Similarly, Sandoz are aware of the JCV testing service provided by the manufacturer of natalizumab originator, and are unaware of any difficulties in the NHS accessing it. • Given this, Sandoz consider the advice given to the EAG that funded JCV testing is not widely available to be inaccurate and request that the Appraisal Committee meeting be presented with economic analysis that exclude the cost	We followed independent clinical opinion for the base case. Explored in “"Scenario 3. Sensitivity including JCV testing”. This excludes the one-off cost of £247 associated with JCV testing for the natalizumab IV and SC interventions, but includes it for natalizumab biosimilar IV. This had limited impact on conclusions.

Page No. (Paragraph)	Company Comment	EAG response
	of JCV testing from the model	

NICE National Institute for Health and Care Excellence

MerckSerano Comments

Comment	Response
Incorrect information about cladribine Throughout the External Assessment report, Merck Serono have noticed inconsistencies and mistakes regarding the evidence and data for cladribine tablets. Some of these inconsistencies, especially regarding the data informing the NMA have greatly impact the NMA results, leading to misleading conclusions regarding the comparative efficacy of cladribine tablets.	See responses to individual comments below.
Serious adverse events (SAEs) pg. 24: In the EAG report, it has been mistakenly stated that no data were available for cladribine for SAEs. In the pivotal CLARITY study by Giovannoni et al 2010, SAEs for cladribine have been reported (*Giovannoni, G., Comi, G., Cook, S., Rammohan, K., Rieckmann, P., Sørensen, P.S., Vermersch, P., Chang, P., Hamlett, A., Musch, B. and Greenberg, S.J., 2010. A placebo-controlled trial of oral cladribine for relapsing multiple sclerosis. New England Journal of Medicine, 362(5), pp.416-426.)* Pg.307, Table 55: It has been mistakenly stated that no SAEs were reported for cladribine. In the pivotal CLARITY study of Giovannoni et al 2010, SAEs for cladribine have been reported (*Giovannoni, G., Comi, G., Cook, S., Rammohan, K., Rieckmann, P., Sørensen, P.S., Vermersch, P., Chang, P., Hamlett, A., Musch, B. and Greenberg, S.J., 2010. A placebo-controlled trial of oral cladribine for relapsing multiple sclerosis. New England Journal of Medicine, 362(5), pp.416-426.)* Based on the above, the NMA should be revised, and results should be updated throughout the report.	Data on SAEs has been added and analysis has been updated
6-month CDP of cladribine versus placebo NMA results Pg.74: In Figure 6, the hazard ratio (HR) and 95% confidence (CI) for cladribine reported in the fixed effects NMA seems incorrect. The HR (95% CI) from the CLARITY study is 0.53 (0.36-0.79) as reported in Figure 2 from the post-hoc analysis of the CLARITY study by Giovannoni et al. 2018. (*Giovannoni, G.,*	Data for CDP6 in RRMS population had been extracted from table 2, Giovannoni G, Cook S, Rammohan K, et al. Sustained disease-activity-

Comment	Response
Soelberg Sorensen, P., Cook, S., Rammohan, K.W., Rieckmann, P., Comi, G., Dangond, F., Hicking, C. and Vermersch, P., 2019. Efficacy of Cladribine Tablets in high disease activity subgroups of patients with relapsing multiple sclerosis: A post hoc analysis of the CLARITY study. Multiple Sclerosis Journal, 25(6), pp.819-827.) Therefore it seems highly unlikely that this NMA could result in such a drastically different HR for time to CDP6 for cladribine vs. placebo compared to the CLARITY Phase III study. This result is also misaligned with reported HRs for CDP6 for cladribine vs. placebo in previously published network meta-analyses (Siddiqui, M. K., Khurana, I. S., Budhia, S., Hettle, R., Harty, G., & Wong, S. L. (2017). Systematic literature review and network meta-analysis of cladribine tablets versus alternative disease-modifying treatments for relapsing–remitting multiple sclerosis. Current Medical Research and Opinion, 34(8), 1361–1371). Pg. 104, Table 12: HRs and 95% CrI for the HARRMS population for cladribine against placebo reported in this section are incorrect. In the HARRMS population, CPD6 should be 0.18 (0.08-0.44) as reported in Giovannoni et al. 2018. (*Giovannoni, G., Soelberg Sorensen, P., Cook, S., Rammohan, K.W., Rieckmann, P., Comi, G., Dangond, F., Hicking, C. and Vermersch, P., 2019. Efficacy of Cladribine Tablets in high disease activity subgroups of patients with relapsing multiple sclerosis: A post hoc analysis of the CLARITY study. Multiple Sclerosis Journal, 25(6), pp.819-827.)* *Pg. 104, Table 12, Pg.300, Table 51 and Pg.303, Table 52: It has been incorrectly stated that HRs and 95% CI for CDP6 for cladribine against placebo are not reported. As presented in the study of Giovannoni et al. 2018., the CDP6 of cladribine versus placebo is 0.53 (0.36-0.79) as shown in Figure 2 of the paper. (Giovannoni, G., Soelberg Sorensen, P., Cook, S., Rammohan, K.W., Rieckmann, P., Comi, G., Dangond, F., Hicking, C. and Vermersch, P., 2019. Efficacy of Cladribine Tablets in high disease activity subgroups of patients with relapsing multiple sclerosis: A post hoc analysis of the CLARITY study. Multiple Sclerosis Journal, 25(6), pp.819-827.)* *Based on the above, the NMA should be revised and results should be updated throughout the report.*	free status in patients with relapsing-remitting multiple sclerosis treated with cladribine tablets in the CLARITY study: a post-hoc and subgroup analysis. Lancet Neurol. 2011;10(4):329-337, where we used number of participants free of disease progression to calculate number of patients with the outcome. We agree that the suggested result is the correct one to be used, so the EAG is thankful for this suggestion and we will update to use this instead. We will also update table 12 with HR and CI to reflect this change. DATA for CDP3 and CDP6 in HARRMS population was taken from table 3 in Vermersch P, Galazka A, Dangond F, et al. Efficacy of cladribine tablets in high disease activity patients with relapsing multiple sclerosis: post hoc analysis of subgroups with and without prior disease-modifying drug treatment. Curr Med Res

Comment	Response
	Opin. 2021;37(3):459-464.Prior-DMD group. We consider this subpopulation to be the closest to the HARRMS definition used in this review. We consider the HRA+DAT population is not adequate because it includes patients who were DMD naïve at study enrolment.
3-month CDP of cladribine versus placebo Pg. 104, Table 12: For HARRMS, CDP3 for cladribine tablets versus placebo should be 0.28 (0.15-0.54) as reported in the Supplementary Figure 1 in Giovannoni et al. 2018. Additionally, for the general RRMS population, CDP3 for cladribine tablets versus placebo should be 0.59 (0.43-0.82) as reported in the Supplementary Figure 1 in Giovannoni et al. 2018. (*Giovannoni, G., Soelberg Sorensen, P., Cook, S., Rammohan, K.W., Rieckmann, P., Comi, G., Dangond, F., Hicking, C. and Vermersch, P., 2019. Efficacy of Cladribine Tablets in high disease activity subgroups of patients with relapsing multiple sclerosis: A post hoc analysis of the CLARITY study. Multiple Sclerosis Journal, 25(6), pp.819-827.)*	See previous comment about data in HARRMS population.
MRI outcomes Pg. 82: In the report, it is stated that "*Data were only available for T2 lesions for interferon beta 1a (SC22) and so this was only included for this outcome".* Merck Serono would like to clarify that relevant data for cladribine tablets are reported on the Supplementary Files in Giovannoni et al. 2018 and in Table 2 of Giovannoni et al 2010. (*Giovannoni, G., Soelberg Sorensen, P., Cook, S., Rammohan, K.W., Rieckmann, P., Comi, G., Dangond, F., Hicking, C. and Vermersch, P., 2019. Efficacy of Cladribine Tablets in high disease activity subgroups of patients with relapsing multiple sclerosis: A post hoc analysis of the CLARITY study. Multiple Sclerosis Journal, 25(6), pp.819-827; Giovannoni, G., Comi, G., Cook, S., Rammohan, K.,*	With this sentence "*Data were only available for T2 lesions for interferon beta 1a (SC22) and so this was only included for this outcome",* we meant that studies evaluating interferon beta 1a (SC22) only reported data for T2 lesions and not T1, we agree the

Comment	Response
Rieckmann, P., Sørensen, P.S., Vermersch, P., Chang, P., Hamlett, A., Musch, B. and Greenberg, S.J., 2010. A placebo-controlled trial of oral cladribine for relapsing multiple sclerosis. New England Journal of Medicine, 362(5), pp.416-426.) Pg.304, Table 53: Merck Serono is unclear which CLARITY trial publication was used to extract proportion of patients with lesions on MRI for cladribine tablets. We would like to refer the EAG to the Supplementary Table 1 of Giovannoni et al. 2018	sentence might be constructed better to avoid misunderstandings and has been amended in the text. Data for MRI lesions for cladribine tablets had been included and taken from Table 1, Giovannoni et al 2011 {#1245}. We consider Supplementary Table 1 of Giovannoni et al. 2018 is not adequate because it reports MRI lesions at baseline, not as an outcome, and table 2 of Giovannoni et al. 2010 reports number of lesions and not number of patients with lesions, which is the outcome being assessed.
Cost-effectiveness model of cladribine Pg. 114: The report stated incorrectly that the model used for TA616 "*simulates a cohort of patients over a lifetime progressing through 10 RRMS & 10 SPMS EDSS health states leading up to death."* Please note that in TA616, the structure of the model comprised 11 health states: 10 Expanded Disability Status Scale (EDSS) states and a single state for death from all causes.	Updated the report.
Pg. 358, Table 91: Similarly, in Table 91, under the column 'outcomes and sources of data' for TA616, it has mistakenly been reported that *"Converting from RRMS to SPMS from the London, Ontario MS database supplemented by the EXPAND trial."* Please note that this was not the case in TA616, as only 11 health states were reported and no SPMS states were included. Therefore, this information is inaccurate.	Updated the report.

Comment	Response
Pg. 326, Table 92: Information regarding TA616 should be revised based on the previous comments. In addition, it was also indicated incorrectly that in TA616, no treatment waning was applied: "*treatment discontinuation as a proxy to waning to as in previous appraisals."* Equal waning of treatment effectiveness for cladribine and all comparators was applied in the model submitted for TA616.	Updated the report.
Costs of cladribine Pg 127, Table 20: The annual treatment acquisition cost for cladribine is incorrectly reported. The annual treatment cost should be £25,953 as the cost of cladribine is dependent on the weight of the cohort, with dosing based on a target dose in milligrams per kilogram per dose. The dose of cladribine tablets is modelled based on the weight distribution of the cohort multiplied by the number of tablets needed to treat people within each weight class. Pg 130, Table 22: The resource use for cladribine tablets in Year 2 onwards is incorrect. This should be revised to reflect: 1 neurology visit instead of 3 neurology visits as per the NHS clinical practice and as indicated in the TA616 Committee papers. (https://www.nice.org.uk/guidance/ta616/evidence/committee-papers-for-ta493-pdf-7021081261)	Updated the acquisition cost in report and model. Number of visits is 3 because there are 3 blood tests and we assume these are taking place in tertiary care as per our clinical advisors.
Baseline characteristics for HARRMS population Pg 287, Table 46: Merck Serono is unclear which publication was used to extract data on baseline participant details for the HARRMS population in CLARITY since the reference reported does not include information for the HARRMS population. We would like to refer the EAG to the Supplementary Table 1 of Giovannoni et al. 2018 (*Giovannoni, G., Soelberg Sorensen, P., Cook, S., Rammohan, K.W., Rieckmann, P., Comi, G., Dangond, F., Hicking, C. and Vermersch, P., 2019. Efficacy of Cladribine Tablets in high disease activity subgroups of patients with relapsing multiple sclerosis: A post hoc analysis of the CLARITY study. Multiple Sclerosis Journal, 25(6), pp.819-827).*	DATA for baseline characteristics for HARRMS population was taken from table 3 in Vermersch P, Galazka A, Dangond F, et al. Efficacy of cladribine tablets in high disease activity patients with relapsing multiple sclerosis: post hoc analysis of subgroups with and without prior disease-modifying

Comment	Response
	drug treatment. Curr Med Res Opin. 2021;37(3):459-464.Prior-DMD group. See previous comment on subpopulation used for HARRMS.
Definition of relapse Pg. 290, Table 47: In the table the definition of relapse from the CLARITY study is incorrect. Based on Giovannoni et al. 2011 and on clincaltrials.gov, a qualifying relapse was defined as: "A qualifying relapse was defined as an increase of 2 points in at least one functional system of the expanded disability status scale (EDSS) or an increase of 1 point in at least two functional systems (excluding changes in bowel or bladder function or cognition) in the absence of fever, lasting for at least 24 hours and to have been preceded by at least 30 days of clinical stability or improvement, which is the definition you have." Therefore, the table under the EDSS column should be updated to: "EDSS increase >2 points in at least one functional system or an increase >1 point in at least at least two functional systems (excluding changes in bowel or bladder function or cognition)".	This has been corrected as follows (wording consistent with other wording in table): EDSS ⩾1 on two functional scores or ⩾2 on one
Relapse rates for cladribine Pg. 297, Table 49: In Table 49, Merck Serono is unclear which publication was used to extract the relapse rates (95%CI) for both cladribine and placebo. As per the notes under the table "unshaded indicates studies that did not report CIs." However, for cladribine tablets CIs in the table are reported.	Relapse rates were extracted (including CI) from Giovannoni, G., Comi, G., Cook, S., Rammohan, K., Rieckmann, P., Sørensen, P.S., Vermersch, P., Chang, P., Hamlett, A., Musch, B. and Greenberg, S.J., 2010. A placebo-controlled trial of oral cladribine for relapsing multiple sclerosis. New England Journal of Medicine, 362(5), pp.416-426.), Table 2. We did not

Comment	Response
	find any report of the relapse rate ratio plus 95%CI, so these were calculated by the EAG.
HRQoL for cladribine Pg. 311, Table 57: In Table 57, can the EAG clarify where these data were extracted from.	Data on HRQoL was extracted from Afolabi D, Albor C, Zalewski L, Altmann DR, Baker D, Schmierer K. Positive impact of cladribine on quality of life in people with relapsing multiple sclerosis. Mult Scler. 2018;24(11):1461-1468, supplementary table S1

Natalizumab and Tyruko (natalizumab biosimilar) for treating highly active relapsing-remitting multiple sclerosis after at least one disease modifying therapy: a systematic review and economic model

ADDENDUM

Produced by: Bristol Technology Assessment Group

Handling of information from the company submissions

Assessment of clinical effectiveness

All information submitted by the company was reviewed by the EAG to determine whether any studies referenced in the submission fulfilled inclusion criteria for the review (section 4.1 of the EAG report). These specified that to be included studies had to be randomised controlled trials conducted in a population with RRMS. Studies were required to compare one of the eligible interventions to an alternative eligible intervention, or to placebo, so that only studies that were informative for the network were included. Studies that only compared different doses, modes of administration, or manufacturers of the same intervention were excluded, unless these were needed to create a connected network.

The EAG also reviewed the company submission to determine whether these included any data not available in published sources, including previous technology appraisals.

This approach is summarised in the methods section of the report (section 4.2.1):

"NICE requested submissions from Companies with technologies in scope for this appraisal (See Table 3). We checked the submissions for studies (and study data) which align with our inclusion criteria. Any studies identified through this process were tabulated to show where they contributed to our review or why they were excluded (Appendix 2)."

All RCT evidence included in the company submissions was also identified by the EAGs literature searches; no additional relevant information was included in the company submissions beyond what was available in published sources. This is reported in section 5 of the report:

"The submissions from the manufacturers for the two drugs of interest for this appraisal (Biogen and Sandos) did not include any relevant studies that we had not identified in our searches – studies included in these submissions, review decision, and reasons for exclusion (where appropriate) are summarised in Table 39 and Table 40 (Appendix 3)."

The company submission included some additional evidence that did not fulfil inclusion criteria for the review. Details on whether each of the studies included in the company submission were eligible for inclusion in the clinical effectiveness review, with reasons for exclusion as appropriate, are outlined in Table 39 (studies included in the Biogen submission) and Table 40 studies included in the Sandoz submission) in Appendix 2.

Studies that did not fulfil the pre-specified review inclusion criteria were not critiqued in detail. However, the EAG do draw on these in the discusion section of the report (section 8.1.1) in the context of evidence included in our review, as follows:

"All trials of natalizumab evaluated natalizumab administered intravenously - there were no studies of natalizumab administered subcutaneously. We did not identify any studies that compared subcutaneous administration of natalizumab with another intervention of interest for this appraisal. We are aware of a small number of trials that have compared different modes of administration of natalizumab, but none met inclusion criteria for our review. DELIVER compared the pharmacokinetics and pharmacodynamics of single subcutaneous or intramuscular 300 mg doses of natalizumab with IV 300 mg doses in patients with MS with a short follow-up duration of 24 weeks and REFINE compared switching to different dosing regimens in stable patients with RRMS who were treated with natalizumab. This study did not meet inclusion criteria for our review as all participants were already receiving natalizumab. These two studies found that natalizumab administered as a 300 mg SC injection every 4 weeks was comparable to 300 mg IV infusion natalizumab every 4 weeks in terms of ARR and CDP3 at week 60 as well as for pharmacokinetics, pharmacodynamics, and safety outcomes."

"In addition to the data from RCTs in people with HARRMS, there is some evidence from non-randomised studies on the effectiveness of natalizumab in people with HARRMS; these studies were not included in our SLR and NMA as our inclusion criteria specified that only RCTs were eligible. A recent targeted literature review and meta-analysis of natalizumab for the treatment of highly active RRMS included studies in adults (≥ 18 years) with a confirmed diagnosis of RRMS who had an unchanged or increased relapse rate compared with the previous year, failed to respond to a full and adequate course of disease modifying therapy (DMT), and had experienced at least one relapse in the previous year while on therapy. They included 16 non-randomised studies that compared natalizumab to interferon beta, glatiramer acetate, teriflunomide, dimethyl fumarate and fingolimod and 11 case series of people treated with natalizumab. Data in the HARRMS population are also available for the TOP study, the largest real world study of

natalizumab, that evaluated the long-term safety and efficacy of natalizumab in 6321 patients (134 UK patients) with RRMS with a follow-up pf 15 years. 151 A post-hoc subgroup analysis in a subset of patients with HARRMS, defined as those who had received prior treatment with ≥1 DMT and had experienced 1 relapse reported similar findings to the findings in the general RRMS population of a reduction of over 90% compared to the year before starting natalizumab. These findings support natalizumab improving outcomes for patients with RRMS and HARRMS, but do not provide a comparison with other interventions."

Assessment of cost effectiveness

Assumptions in the EAG model and manufacturer submitted cost-comparisons

Both Biogen and Sandoz submitted cost-comparisons. We considered the assumptions of the manufacturer submission when developing our model. Table 1 presents a comparison of manufacturer costing assumptions with the EAG base case. Our assumptions were formed after reviewing TAs within the scope and discussions with clinical advisors, and these are detailed in the main report. Note that interventions and comparators were restricted and not aligned with the PICOS of our assessment. Treatment list prices are published list prices by the British National Formulary and not considered in the comparison.

Table 1 Comparison of costing assumptions from EAG's base case with manufactures' submissions

Treatments	**EAG base case**	**Biogen**	**Sandoz**	**Rationale behind EAG base case assumptions**
	Natalizumab-IV Natalizumab-biosimilar-IV Natalizumab-SC	Natalizumab-IV Natalizumab-SC	Natalizumab-biosimilar-IV	
Comparators	Alemtuzumab Cladribine tablets Fingolimod Ocrelizumab Ofatumumab Ponesimod Interferon beta 1a 30 mcg Interferon beta 1a 22 mcg Interferon beta 1a 44 mcg Peginterferon beta 1a 125 mcg Glatiramer acetate 20 mg Glatiramer acetate 40 mg	None	Natalizumab-IV Natalizumab-SC Ocrelizumab Ofatumumab	As per scope.
Cost-effectiveness analysis	yes	no	no	-
No of doses per year	yes	yes	yes	As per clinical advisors.

Treatments	EAG base case	Biogen	Sandoz	Rationale behind EAG base case assumptions
	Natalizumab-IV Natalizumab-biosimilar-IV Natalizumab-SC	Natalizumab-IV Natalizumab-SC	Natalizumab-biosimilar-IV	
Treatment administration (HRG) costing –day case	yes	no	yes	Day case is required as per clinical advisors.
Treatment administration activity-based costing: • Treatment administration time in minutes • Treatment preparation time in minutes • Nurse hourly rates • equipment costs per administration • number of patients per nurse	no	yes	no	
Reduction in administration time	no	yes	no	IV and SC patients are treated the same as per clinical advisors.
Reduction in observation: • time • number of patients	no	yes	no	
Annual treatment Monitoring visits with health care professionals and associated costs (in patient/out patient care, tests, etc..)	yes	no	no	Required as per clinical advisors.