NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Siponimod for treating secondary progressive multiple sclerosis [ID1304]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Siponimod for treating secondary progressive multiple sclerosis [ID1304]

Contents:

The following documents are made available to consultees and commentators:

The **final scope** and **final stakeholder list** are available on the NICE website

1. **Company submission summary** from Novartis Pharmaceuticals

2. **Clarification questions and company responses**

3. **Patient group, professional group and NHS organisation submission** from:
   a. Multiple Sclerosis Society
   b. Multiple Sclerosis Trust
   c. Association of British Neurologists
   d. UK Multiple Sclerosis Specialist Nurse Association

4. **Expert personal perspectives** from:
   a. Mrs C Wilkinson – clinical expert, nominated by UK Multiple Sclerosis Specialist Nurse Association
   b. Mrs J Krarup – patient expert, nominated by Multiple Sclerosis Society
   c. Mrs C Smith– patient expert, nominated by Multiple Sclerosis Trust
   d. Dr M Craner – clinical expert, nominated by Multiple Sclerosis Trust
   e. Malcolm Qualie - commissioning expert, nominated by NHS England

5. **Evidence Review Group report** prepared by Warwick Evidence

6. **Evidence Review Group report – factual accuracy check**

7. **Final Technical report**

8. **Technical engagement response from company**
   a. **Appendix A**
   b. **Appendix B**

9. **Technical engagement responses from experts:**
   a. Mrs C Smith– patient expert, nominated by Multiple Sclerosis Trust

10. **Technical engagement responses from consultees and commentators:**
    a. Multiple Sclerosis Trust
    b. ABN
    c. Roche

11. Evidence Review Group critique of company response to technical engagement prepared by Warwick Evidence

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

Single technology appraisal

Siponimod for treating secondary progressive multiple sclerosis [ID1304]

Document B

Company evidence submission

September 2019

File name	Version	Contains confidential information	Date
NICE Siponimod Document B	**Final**	**Yes**	**11/09/2019**

Instructions for companies

This is the template for submission of evidence to the National Institute for Health and Care Excellence (NICE) as part of the single technology appraisal (STA) process. Please note that the information requirements for submissions are summarised in this template; full details of the requirements for pharmaceuticals and devices are in the user guide.

This submission must not be longer than 150 pages, excluding appendices and the pages covered by this template. If it is too long it will not be accepted.

Companies making evidence submissions to NICE should also refer to the NICE guide to the methods of technology appraisal and the NICE guide to the processes of technology appraisal.

In this template any information that should be provided in an appendix is listed in a box.

Highlighting in the template (excluding the contents list)

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Grey highlighted text in the footer does not work as an automatic form field, but serves the same purpose – as prompt text to show where you need to fill in relevant details. Replace the text highlighted in [grey] in the header and footer with appropriate text. (To change the header and footer, double click over the header or footer text. Double click back in the main body text when you have finished.)

Contents

Tables and figures

Abbreviations

Abbreviation	Definition
9-HPT	Nine-hole peg test
ABN	Association of British Neurologists
AE	Adverse event
ARR	Annualised relapse rate
BNF	British National Formulary
BSC	Best supportive care
BVMT-R	Brief visuospatial memory test-revised
CDP	Confirmed disability progression
CI	Confidence interval
CNS	Central nervous system
CSR	Clinical study report
CTCAE	Common terminology criteria for adverse events
CYP2C9	Cytochrome P450 2C9
DMF	Dimethyl fumarate
DMT	Disease-modifying therapy
DSU	Decision Support Unit
ECG	Electrocardiogram
EDSS	Expanded disability status scale
EE	Effect estimate
EMA	European Medicines Agency
eMIMS	Electronic Monthly Index of Medical Specialities
EQ-5D-3L	European quality of life 5-dimensions, 3-levels
FAS	Full analysis set
FDA	Food and Drugs Administration
GA	Glatiramer acetate
HR	Hazard ratio
HRQoL	Health-related quality of life
HSU	Health state utility
HTA	Health Technology Assessment
ICER	Incremental cost-effectiveness ratio
ICER	Institute for Clinical and Economic Review
ICH	International Conference on Harmonisation
IFN	Interferon
IM	Intramuscular
IPCW	Inverse probability censoring weight
IPD	Individual patient data
ITC	Indirect treatment comparison
ITT	Intention-to-treat
IV	Intravenous

LCVA	Low contrast visual acuity
LYG	Life-years gained
MAIC	Matching-adjusted indirect treatment comparison
MFIS	Modified fatigue impact scale
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
MSFC	Multiple sclerosis functional composite
MSIS-29	Multiple sclerosis impact scale
MSM	Multi-state modelling
MSSS	Multiple sclerosis severity scale
MSWS-12	Multiple sclerosis walking scale
MTA	Multiple technology assessment
NH	Natural history
NHS	National Health Service
NMA	Network meta-analysis
ONS	Office for National Statistics
OR	Odds ratio
PAS	Patient Access Scheme
PASAT	Paced auditory serial addition test
PBVC	Percentage brain volume change
PK	Pharmacokinetics
PPMS	Primary progressive multiple sclerosis
PRO	Patient reported outcome
PS	Principal stratum
PSA	Probabilistic sensitivity analyses
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
Q2D	Every other day
Q4W	Once every four weeks
QALY	Quality-adjusted life-year
QD	Once daily
QW	Once weekly
RCT	Randomised controlled trial
RMS	Relapsing multiple sclerosis
RPSFT	Rank-preserving structural failure time
RRMS	Relapsing-remitting multiple sclerosis
RSS	Risk sharing scheme
S1P	Sphingosine-1-phosphate
SAE	Serious adverse event
ScHARR	School of Health and Related Research
SD	Standard deviation
SDMT	Symbol digit modalities test

SE	Standard error
SLR	Systematic literature review
SMD	Standardised mean difference
SmPC	Summary of product characteristics
SOC	Systems organ class
SPMS	Secondary progressive multiple sclerosis
T25FW	Timed 25-foot walk test
TEAE	Treatment-emergent adverse events
TIW	Three times weekly
TSD	Technical support document
VAS	Visual analogue scale
WTP	Willingness to pay

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

B.1.1 *Decision problem*

The submission covers the technology's full marketing authorisation for this indication.

The decision problem addressed by this submission is summarised 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	People with SPMS	Adults with SPMS	Siponimod is anticipated to be licensed for adult patients with SPMS
Intervention	Siponimod (Mayzent®)	Siponimod (Mayzent®)	N/A
Comparator(s)	• Established clinical management, including disease-modifying therapies used outside their marketing authorisations • Interferon β-1b for patients with active disease, evidenced by relapses	• Established clinical management, comprising ongoing RRMS DMTs • Interferon β-1b for patients with active disease, evidenced by relapses and/or MRI activity	• Patients start DMTs in RRMS and continue to use them during the transition, while being suspected of SPMS • Interferon β-1b is currently the only option specifically for treatment for patients with SPMS, and is therefore considered the most relevant comparator within established clinical management • Activity in clinical practice includes MRI activity; the interferon β-1b label wording "evidenced by relapses" reflects practice ~15–20 years ago
Outcomes	• Disability (for example, EDSS) • Disease progression • Relapse rate and severity (for those with active disease) • Symptoms of MS such as fatigue, cognition and visual disturbance • Freedom from disease activity • Mortality • Adverse effects of treatment • Health-related quality of life	• Disability: o EDSS • Disease progression: o Time to 3-month CDP, defined as a 1-point increase in EDSS if the baseline score was 3.0-5.0, or a 0.5-point increase if the baseline score was 5.5-6.5 o Time to 6-month CDP o Change from baseline in T2 lesion volume • Relapse rate and severity: o ARR	Measures of relapse rate and severity are assessed for all patients, regardless of disease activity at baseline. [redacted]% of patients identified as non-Active at baseline in the placebo arm, then went on to exhibit relapses in the trial, highlighting the difficulties in accurately defining a patient as non-Active.

		○ Time to first relapse ○ Proportion of relapse-free patients • Symptoms of MS ○ Time to 3-month confirmed worsening of at least 20% from baseline in the T25FW ○ Change in score on the patient-reported MSWS-12 ○ Cognitive measures: PASAT; SDMT; BVMT-R • Freedom from disease activity ○ Number of T1 gadolinium-enhancing lesions ○ Number of new or enlarging T2 lesions ○ Percentage change in brain volume from baseline • Mortality • Safety and tolerability (adverse effects of treatment) • HRQoL ○ EQ-5D ○ MSIS-29	
Subgroups to be considered	• Active disease, evidenced by relapses	• Active SPMS, as evidenced by relapse and/or MRI activity	• Activity in clinical practice includes MRI activity

Abbreviations: ARR: annualised relapse rate; BVMT-R: brief visuospatial memory test-revised; CDP: confirmed disability progression; DMT: disease modifying therapy; EDSS: Expanded Disability Status Scale; EQ-5D: European quality of life five-dimensions scale; HRQoL: health-related quality of life; MRI: magnetic resonance imaging; MS: multiple sclerosis; MSIS-29: multiple sclerosis impact scale; MSWS-12: multiple sclerosis walking scale; N/A: not applicable; PASAT: paced auditory serial addition test; RRMS: relapsing-remitting multiple sclerosis; SDMT: symbol digit modalities test; SPMS: secondary progressive multiple sclerosis; T25FW: timed 25-foot walk test.
Source: NICE scope for siponimod.[1]

B.1.2 *Description of the technology being appraised*

A description of the technology appraised is summarised in Table 2. The summary of product characteristics (SmPC) for siponimod is provided in Appendix C.

Table 2: Technology being appraised

UK approved name and brand name	Siponimod (Mayzent®)
Mechanism of action	Siponimod is a selective agonist of sphingosine-1-phosphate (S1P) receptors $S1P_1$ and $S1P_5$. Siponimod selectively binds to circulating lymphocytes, which reversibly inhibits egress of lymphocytes from the lymph nodes, leading to a reduction in disease activity.
Marketing authorisation/CE mark status	EMA marketing authorisation is expected in December 2019.
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	The licence wording is currently anticipated to be: 'Mayzent® is indicated for the treatment of adult patients with secondary progressive multiple sclerosis.' Siponimod has the following contraindications: • Immunodeficiency syndrome • History of progressive multifocal leukoencephalopathy or cryptococcal meningitis • Active malignancies • Severe liver impairment (Child-Pugh class C) • Patients who in the previous 6 months had a myocardial infarction, stroke/transient ischaemic attack, unstable angina pectoris, decompensated heart failure (requiring inpatient treatment), or New York Heart Association (NYHA) class III/IV heart failure (see SmPC for details) • Patients with second-degree Mobitz type II atrioventricular block, third-degree atrioventricular block, sino-atrial heart block or sick-sinus syndrome, if they do not wear a pacemaker • Patients homozygous for CYP2C9*3 (CYP2C9*3*3) genotype (poor metaboliser) • Hypersensitivity to the active substance or to peanut, soya, or any of the excipients listed in the SmPC • During pregnancy and in women of childbearing potential not using effective contraception
Method of administration and dosage	The recommended maintenance dose for siponimod is one 2 mg tablet taken once daily with or without food. Treatment has to be started with a titration pack that lasts for 5 days. Treatment starts with 0.25 mg once daily on Days 1 and 2, followed by once-daily doses of 0.5 mg on Day 3, 0.75 mg on Day 4, and 1.25 mg on Day 5, to reach the patient's prescribed maintenance dose of Mayzent starting on Day 6. The same titration pack is used for both 1 and 2 mg maintenance doses; this may change dependent upon the final EMA guidance. • During the first 6 days of treatment, the recommended daily dose should be taken once daily in the morning with or without

	food • During the first 6 days of treatment, if a titration dose is missed on one day treatment needs to be re-initiated with a new titration pack If maintenance treatment is interrupted for four or more consecutive daily doses, Mayzent needs to be re-initiated with a new titration pack. Before initiation of treatment, patients must be genotyped for CYP2C9 to determine their CYP2C9 metaboliser status:[2] • In patients with a CYP2C9*3*3 genotype (approximately 0.3−0.4% of the population), siponimod should not be used • In patients with a CYP2C9*2*3 (approximately 1.4−1.7% of the population) or *1*3 genotype (0−12% of the population), the recommended maintenance dose is 1 mg taken once daily (four tablets of 0.25 mg) • Dosage adjustment to 1 mg daily may be considered in patients with a CYP2C9*2*2 genotype for combination treatment with moderate CYP2C9/strong CYP3A4 inhibitors (e.g. fluconazole) because of an expected increase in siponimod exposure • The recommended maintenance dose of siponimod in all other CYP2C9 genotype patients is 2 mg
Additional tests or investigations	• Before initiation of treatment, patients must be genotyped for CYP2C9 to determine their CYP2C9 metaboliser status. • As a precautionary measure, patients with sinus bradycardia, first- or second-degree [Mobitz type I] atrioventricular block, or a history of myocardial infarction or heart failure, should be observed for a period of 6 hours after the first dose of siponimod for signs and symptoms of bradycardia.
List price and average cost of a course of treatment	List price of siponimod: £[redacted] per pack of 28 tablets Annualised cost of siponimod at list price: £[redacted] per annum
Patient access scheme (if applicable)	A confidential simple discount Patient Access Scheme (PAS) provides siponimod at a fixed net price of £[redacted] per pack of 28 tablets. This represents a [redacted] discount from the list price. Annualised cost of siponimod at with-PAS price: £[redacted]

Abbreviations: CYP2C9: cytochrome P450 2C9; EMA: European Medicines Agency; NYHA: New York Heart Association; PAS: Patient Access Scheme; S1P: sphingosine-1-phosphate; SmPC: Summary of Product Characteristics.
Source: Kappos et al. 2018;[3] Novartis Data on File (draft SmPC for siponimod).[2]

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

B.1.3.1 Secondary Progressive Multiple Sclerosis

Disease overview and pathogenesis

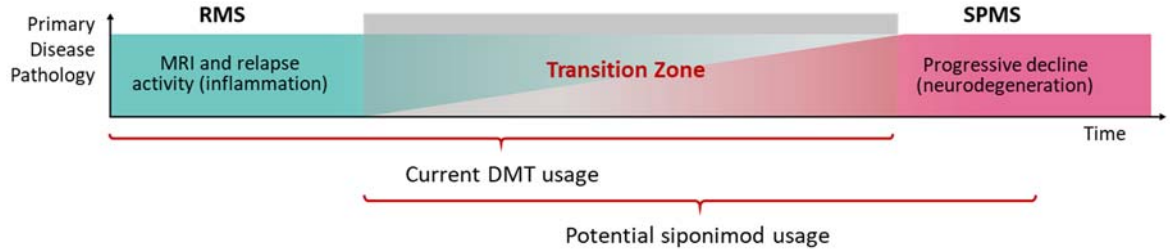
Multiple sclerosis (MS) is a chronic, neurodegenerative, autoimmune disorder in which the body's own immune system attacks the myelin sheath of nerve axons in the central nervous system (CNS).[4, 5] It is characterised by inflammation of nerve tissue in the CNS, leading to destruction of

myelin sheaths and hence a slowing or even blocking of nerve transmission to and from the brain and spinal cord, affecting loss of functionality such as movement and sensation and irreversible progression of disability.[4, 6]

Approximately 110,000 people in the UK have MS, with around 5,000 people diagnosed each year, equating to roughly 100 new patients a week.[7] The overall pathophysiology of MS is complex and not completely understood. The major processes underlying the disease are thought to be inflammation and neurodegeneration.[8] MS is a highly heterogenous disease but three broad patterns of disease have been identified, classified by the pattern and frequency of relapses and the rate of progression of the disease: relapsing-remitting MS (RRMS); secondary progressive MS (SPMS); and primary progressive MS (PPMS).[9] The disease courses of MS can be seen as a continuum incorporating an intense focal inflammatory component in early RRMS and more neurodegenerative features alongside chronic inflammation and axon loss in progressive forms of MS (SPMS and PPMS) (Figure 1).[8, 10] Nonetheless, both inflammation and neurodegeneration are present in all forms of the disease.

At the point of diagnosis, the majority of patients (around 85%) exhibit a relapsing-remitting pattern, with periods of relapse where symptoms flare up aggressively followed by periods of remission.[11, 12] The majority of patients with RRMS will eventually experience a change in their MS, with fewer or no relapses, but increasing disability and decline in neurological function, reflecting a secondary progressive pattern.[13] The transition from predominantly relapsing forms of MS (RMS) to more progressive forms of MS is gradual and the RRMS and SPMS phenotypes inherently overlap (Figure 1). Consequently, clinicians tend to avoid identifying SPMS in a patient whilst they are plausibly eligible for RRMS disease-modifying therapies (DMTs).[9, 14] It is reported that approximately two-thirds of patients initially diagnosed with RRMS will transition to SPMS within a period of 30 years.[15, 16]

Figure 1. Disease pattern over time for people diagnosed with MS that initially follows a relapsing (RMS) pattern, indicating the gradual change from RMS to SPMS



All DMTs (including siponimod) are limited to EDSS 6.5 due to lack of evidence at EDSS 7.0 or above.
Abbreviations: DMT: disease-modifying therapy; EDSS: Expanded Disability Status Score; MRI: magnetic resonance imaging; RMS: relapsing multiple sclerosis; SPMS: secondary progressive multiple sclerosis.

It is estimated there are around 43,000 people in the UK with SPMS.[17, 18] However, implementation of the definition of SPMS in practice can vary widely due to there being no clear clinical, imaging, immunologic, or pathologic criteria to determine a so-called “transition point” when RRMS converts to SPMS – this reflects the fact that RRMS and SPMS form a continuum (Figure 1).[9, 13, 19, 20] The transition is usually gradual and the diagnosis of SPMS tends to be considered over a number of years and appointments. By definition, SPMS is diagnosed retrospectively by a history of gradual worsening after an initial relapsing disease course, with or without acute exacerbations during the progressive course.[9] Determining disability progression is complicated by the day-to-day fluctuations in the disease which may be impacted by minor illnesses such as colds.[14] It has been reported that a mean of 2.9±0.8 years is a typical length of

time for the uncertainty of whether a patient has transitioned to SPMS.[19] Although guidelines have been designed in an attempt to make the definitions more precise,[9, 12] there is still variation in practice with different clinicians likely to identify SPMS at different times for the same patient, and many clinicians report that their clinic does not use any standardised approach or protocol to identify the transition to SPMS.[14]

Importantly, clinicians tend to continue the use of DMTs in light of suspected SPMS because of uncertainty in making a firm SPMS diagnosis, reluctance to stop treatment given the limited alternative DMT options (see Section B.1.3.3), perceived continued clinical benefit, and patients' fear of disease activity returning upon withdrawal. Because of this, clinicians therefore avoid identifying SPMS in patients for as long as is clinically possible.[14, 21]

Effects of SPMS on patients and carers

The effects of MS vary greatly from patient to patient and from day to day with no clear replicable pattern and a wide range of different symptom types.[13] Symptoms include pain, muscle weakness or spasticity, chronic fatigue, unsteady gait, speech problems, incontinence, visual disturbance and cognitive impairment.[5] One of the most obvious changes patients with MS experience is the decline in mobility, with many patients eventually requiring the use of walking aids or wheelchairs. Symptoms progress and worsen over time, with progressive forms of MS being associated with lower utility values and lower measures of health-related quality of life (HRQoL) than RRMS.[22] Patients with MS are affected by many more symptoms than their physical disability – many symptoms are 'invisible' to those around them.

Diagnosis of MS usually occurs when people are in their 20s and 30s and affects patients for the remainder of their lives.[5] Although MS is not a terminal illness, it is lifelong and, on average, patients live with the condition for 40 to 50 years. MS reduces life expectancy by six to seven years compared with the general population.[5] One contributing factor to this is partially because of the increased risk of depression among patients with MS, leading to an increased risk of suicide.[23-26]

The diagnosis of SPMS brings with it a significant psychological impact for patients: feelings of hopelessness and a perceived loss of independence and control are often experienced by patients due to the requirement to stop treatment and seeming lack of options to prevent further progression.[14, 27] SPMS has been associated with greater distress, lower quality of life, and higher levels of depression and anxiety than in both RRMS and PPMS.[21] Commonly, patients describe the diagnosis of SPMS as bringing up similar feelings as when first diagnosed with MS.[13, 27] Patients become increasingly dependent on caregivers, from both a personal and financial perspective, with research suggesting 85% of people with MS receive support or assistance from friends and family members.[14, 28] Many patients experience a significant drop in confidence, a restriction in activity and limitations in their role in society, including the inability to continue employment. One study reported that only 36% of patients with MS below retirement age were in employment, compared to 74% in the general UK population.[29] Another reported that up to 80% of people with MS stop working within 15 years of the onset of diagnosis and 44% retire early because of the condition.[30]

B.1.3.2 Siponimod

Description of siponimod

Siponimod is an orally administered, potent, and selective small-molecule agonist of sphingosine-1-phosphate (S1P) receptors $S1P_1$ and $S1P_5$.[31, 32] $S1P_1$ and $S1P_5$ receptors are involved in regulation of immunomodulatory/anti-inflammatory, pro-myelinating and neuroprotective effects.[33, 34] Siponimod is a second-generation oral S1P modulator designed using fingolimod as an initial lead structure and optimised for potency at $S1P_1$, selectivity against $S1P_3$, and an improved safety and pharmacokinetics profile.[31] The first dose of fingolimod (a first-generation oral S1P modulator) is associated with a decrease in heart rate and slowing of atrioventricular conduction.[35, 36] Discovery that bradycardia in mice is mediated by the $S1P_3$ receptor[37] led to the development of the selective modulator, siponimod.

Siponimod is a close structural analogue of S1P, a naturally occurring bioactive sphingolipid that plays a key role in the processes relevant to MS, including inflammation and repair.[38, 39] It has been shown that the lymphocytic $S1P_1$ receptor plays a key role in the egress of lymphocytes from lymphoid organs, and agonists of these receptors down-modulate lymphocytic $S1P_1$ to slow the S1P-$S1P_1$-dependent egress into cortical sinuses of the lymph nodes.[40-42]

As well as reducing inflammatory activity (i.e. fewer gadolinium-enhancing lesions and fewer new or enlarging T2 lesions), siponimod also reduces the extent and progression of neurodegeneration (i.e. reduced disability progression and brain atrophy).[43] Notably, a phase III trial of fingolimod vs placebo in patients with PPMS failed to show a significant effect on 3-month confirmed disability progression (CDP), measured by EDSS, 9-hole peg test and timed 25-foot walk (T25FW) test,[44] suggesting siponimod has additional benefits and interactions beyond those of fingolimod.

$S1P_1$ and $S1P_5$ are expressed by neural cells such as astrocytes,[45] oligodendrocytes,[46] microglia and neurons.[47] It has been shown that siponimod readily crosses the blood-brain barrier in mice and hence potentially directly interacts with brain cells.[43, 48] Findings from preclinical studies suggest that siponimod prevents synaptic neurodegeneration,[48] has the potential to promote remyelination in the CNS,[49] and modulates pathways involved in cell survival with subsequent reduction of demyelination.[50]

In one pre-clinical study in mice, siponimod was delivered directly into the brain in order to measure direct neuronal effects.[48] Amelioration of experimental autoimmune encephalomyelitis (EAE, a model of autoimmune driven CNS inflammation) disease score was observed without affecting peripheral $CD3^+$ cell counts, and astrocytosis, microgliosis and neuronal loss were all less severe in siponimod-treated mice.[48] Therefore, siponimod may be considered as neuroprotective, preventing the loss of neurons.[43]

The combined results of pre-clinical and clinical studies suggest that siponimod is not only anti-inflammatory, but also possesses an additional neuroprotective mechanism of action, plausibly providing patients with a longer-term protective effect, rather than solely impacting upon inflammatory disease activity.

EXPAND trial

This submission focusses on the randomised phase III study EXPAND (EXploring the efficacy and safety of siponimod in PAtients with secoNDary progressive multiple sclerosis), which

evaluated siponimod compared to placebo in slowing disability progression in patients with SPMS (see Section B.2 for further details).[3]

Participants were age 18–60 years with a diagnosis of SPMS and documented moderate-to-advanced disability as indicated by an EDSS score of 3.0–6.5 at screening. 26% of patients receiving siponimod and 32% receiving placebo had 3-month CDP (hazard ratio [HR] 0.79, 95% CI 0.65–0.95; relative risk reduction 21%; p=0.013).[3] Sensitivity analysis of this primary endpoint and other clinical and MRI-defined secondary outcomes – notably reduction in brain volume loss (an objective marker of permanent tissue damage) – were consistent with this result. Combined with a similar safety profile to that of other S1P receptor modulators, the EXPAND trial showed siponimod to be a beneficial treatment for patients with SPMS.

Marketing Authorisation and health technology assessment

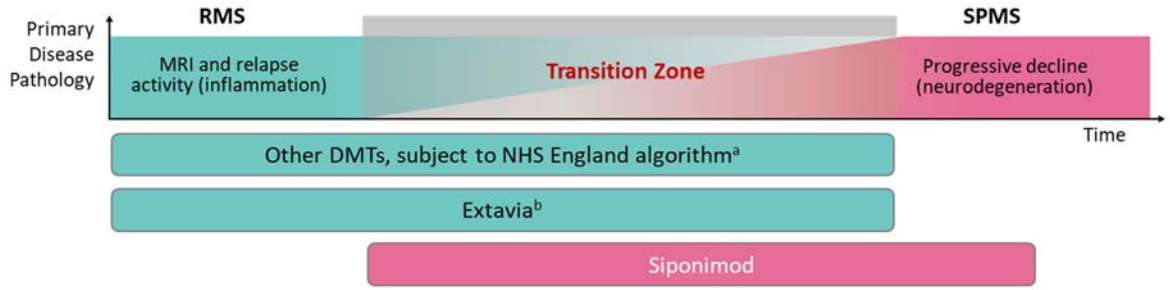
- Marketing Authorisation Application (MAA) was submitted in September 2018
- Committee for Medicinal Products for Human Use (CHMP) opinion is expected in October 2019
- Marketing authorisation is expected to be granted in December 2019

B.1.3.3 Current Treatment Pathway and the Position of Siponimod

A number of DMTs have are recommended by NICE for use in MS, however these almost exclusively apply to patients with RRMS (Figure 2).[51] Interferon β-1b (Extavia®) is the only current option for patients with SPMS, as well as RRMS, but is only recommended in the case of patients experiencing continuing relapses.[52] This recommendation stems from the evidence that interferon β-1b reduces relapse risk in patients with SPMS but has not been shown to be able to significantly slow disability progression versus placebo.[53, 54] As the only current treatment option specifically for patients with SPMS, interferon β-1b is the most relevant comparator for siponimod and as such is considered as the base case comparator in the economic analysis.

Additionally, a number of treatments are licensed for RMS (rather than RRMS) use but the manufacturers did not position their products for relapsing SPMS (rSPMS) in their appraisals. NICE only appraised the treatments in line with the evidence submitted: ocrelizumab is licensed for relapsing forms of MS but is only recommended for use in RRMS (it is also licensed and recommended for PPMS);[55, 56] and cladribine is licensed for patients with highly active RMS but is only recommended for use in RRMS.[57] The label for interferon β-1a (Rebif®) specifically indicates that "efficacy has not been demonstrated in patients with secondary progressive multiple sclerosis without ongoing relapse activity."[58]

Figure 2: Current treatment options for patients with MS[51, 59]



All DMTs (including siponimod) are limited to EDSS 6.5 due to lack of evidence at EDSS 7.0 or above.
[a] Approved DMTs: alemtuzumab; Avonex®; cladribine; dimethyl fumarate; fingolimod; glatiramer acetate; natalizumab; ocrelizumab; Rebif®; teriflunomide.

[b] Subject to relapse criteria. Extavia® is the only current treatment option specifically for patients with SPMS and considered the base case and most relevant comparator for siponimod.
Abbreviations: DMT: disease-modifying therapy; EDSS: Expanded Disability Status Score; MRI: magnetic resonance imaging; NHS: National Health Service; RMS: relapsing multiple sclerosis; SPMS: secondary progressive multiple sclerosis.

There are currently no licensed treatments available for patients with SPMS who do not experience relapses, and there is a significant unmet treatment need for these patients (Figure 2). Due to the hesitancy and uncertainty in identifying SPMS, many patients stay on an RRMS DMT throughout the transition phase to SPMS (Figure 2). Although DMTs for RRMS have not been proven to be effective in SPMS, continuing the DMT is preferred over being left with symptomatic treatment only.[14, 60] Introduction of siponimod would remove the hesitancy for SPMS to be identified in these patients at a much earlier stage and to allow them continued treatment with a DMT proven to be effective for their MS phenotype.

Unmet treatment need

There are currently no licensed or proven treatments for patients with SPMS experiencing disability progression independent of relapses; the only drugs that can be prescribed are for symptom management.[51] Research has revealed that clinicians believe that if a licensed and reimbursed DMT were to become available for SPMS, this would reduce the hesitancy of identifying SPMS in patients.[14, 61]

SPMS is a typically hard-to-treat population, as demonstrated by some of the highly efficacious drugs licensed for RRMS (fingolimod and natalizumab) having failed in progressive MS trials.[44, 62] Although interferon β-1b reduces relapse risk in patients with SPMS, it has been shown to be unable to significantly slow disability progression compared to placebo.[53] Siponimod would be the first treatment to be recommended by NICE that can slow disability progression for patients with SPMS and the first for use in all patients with SPMS.

Starting criteria

While the SmPC does not specify formal starting criteria, based on the inclusion criteria of the EXPAND trial, in the National Health Service (NHS) practice siponimod is expected to be initiated in patients with a history of RRMS, an EDSS between 3.0 and 6.5, and SPMS defined as a progressive increase of disability over at least 6 months.

B.1.4 *Equality considerations*

The technology is unlikely to raise any equality concerns, considering that the technology will not exclude certain patient populations. Introduction of siponimod is not likely to lead to recommendations which differentially impact patients protected by the equality legislation or disabled persons.

B.2 Clinical effectiveness

A systematic literature review (SLR) identified one randomised controlled trial (RCT) for siponimod in the relevant patient population as defined by the NICE scope (EXPAND).

- The results of the EXPAND trial, including data for patient-reported HRQoL outcomes, are presented from the Kappos et al. publication,[3] the interim clinical study report (CSR)[63] and CSR amendment.[64]
- The patient population enrolled was consistent with an SPMS patient population; moderately to severely disabled (median EDSS score of 6.0) and low inflammatory disease activity, and included patients with both Active and non-Active SPMS.
- The primary outcome was the delay to time to 3-month CDP as measured by EDSS.
- The key secondary outcomes looked at the change in baseline in T2 lesion volume and the time to 3-month confirmed worsening of at least 20% from baseline in T25FW.
- Additional secondary outcomes included time to 6-month CDP, relapse-related measures (annualised relapse rate [ARR]; time to first relapse; proportion of relapse-free patients), MRI measures (number of new or enlarging T2 lesions; number of Gd-enhancing T1 lesions; percentage change in brain volume from baseline), cognitive tests, HRQoL and safety (treatment-emergent adverse events [TEAEs]).
- EXPAND was methodologically robust, well reported and considered to be at low risk of bias.
- The results of the EXPAND study are well aligned with the decision problem specified in the NICE scope and the trial results are directly relevant to treatment in NHS clinical practice.

The EXPAND study met its primary endpoint, demonstrating a statistically significant and clinically meaningful improvement in delaying the time to 3-month CDP as measured by EDSS.

- By delaying disability progression, patients are able to maintain their current level of physical and cognitive abilities and their quality of life for longer, for instance by extending the time prior to a patient requiring permanent use of a wheelchair.
- Siponimod displayed a 21.2% risk reduction compared with placebo for time to 3-month CDP (HR 0.79, p=0.0134). Kaplan-Meier estimates indicated that the time to first quartile (25%) of patients experiencing 3-month CDP events was observed approximately 6 months later in patients randomised to siponimod relative to patients randomised to placebo.
- Siponimod treatment also delayed the time to 6-month CDP compared with placebo with a risk reduction of 25.9% (HR 0.74, p=0.0058, unadjusted for multiplicity).
- Delaying the time to 3-month confirmed worsening in T25FW of at least 20% from baseline showed a risk reduction of 6.2% in favour of siponimod, but this did not reach statistical significance. However, T25FW is thought to have suboptimal sensitivity for change in patients with more advanced MS, such as those in the EXPAND trial. Improvement in MS walking scale (MSWS-12) also did not reach statistical significance.
- Siponimod displayed improvement in patients compared with placebo across all MRI outcomes measured: smaller increase in T2 lesion volume; fewer Gd-enhancing T1 lesions; fewer new or newly enlarging T2 lesions; and a smaller decrease in brain volume.
- An improvement in patients taking siponimod compared with placebo was also seen across all relapse-related measures: 55.5% rate reduction for confirmed relapses; delayed time to first relapse; and fewer patients experienced relapses. Combined with the improvements in MRI activity, this demonstrates a reduction in inflammatory activity in these patients.
- [redacted] in HRQoL measures were observed for both the physical MSIS-29 and European quality of life 5-dimensions (EQ-5D) utility scores at Month 12, but these were [redacted] to Month 24, however the apparently [redacted] between-group differences at Month 24

compared with Month 12 should be interpreted in light of the small sample size and higher variability at Month 24 due to the event-driven trial design.

- Siponimod showed a [redacted] compared with placebo for the cognitive measure of the symbol digit modalities test (SDMT) at Month 12, which [redacted] at Month 24, showing [redacted] deterioration in attention, concentration and processing speed.
- Sensitivity analyses to explore the effect of siponimod on CDP, unrelated to the effect on relapses, gave results consistent with the effect on overall population for 3-month CDP (relative risk [RR] [redacted] vs HR 0.79) and 6-month CDP (RR [redacted] vs HR 0.74).[65]
- From the results of the ongoing extension phase of the EXPAND trial, siponimod showed evidence of maintained treatment effect with respect to 6-month CDP after 5.5 years (rank-preserving structural failure time [RPSFT]-adjusted HR [redacted] compared with 0.74 at the end of the core part of the trial).[66]
- Overall, the results of the EXPAND trial clearly demonstrate the clinical efficacy of siponimod in patients with SPMS, with a meaningful delay in disability progression, both in terms of EDSS progression, and MRI and relapse activity.

Reduction in the risk of disability progression with siponimod was consistently observed across all pre-planned subgroups.

- Due to uncertainty at the point of submission as to the final licenced population for siponimod, a specific subgroup population of Active SPMS is additionally presented.
    - The *post hoc* Active SPMS subgroup included patients who experienced relapses in the two years prior to the study and/or who had gadolinium-enhanced T1 lesions at baseline.
    - Siponimod treatment delayed the time to both 3- and 6-month CDP in the *post hoc* Active SPMS subgroup compared with placebo (risk reduction of [redacted]% [p=[redacted]] for 3-month CDP, and [redacted]% [p=[redacted]] for 6-month CDP). These outcomes were [redacted] for the Active SPMS subgroup than for the intention-to-treat (ITT) population.
    - Siponimod also demonstrated an improvement in ARR in the Active SPMS subgroup compared with placebo with a [redacted]% risk reduction, p=[redacted].

In an indirect comparison, siponimod displayed numerically favourable comparisons to [redacted] for time to 3- and 6-month CDP, and ARR ([redacted]).

- An SLR identified 97 publications on 23 unique studies of DMTs in SPMS. Of these, six RCTs, including EXPAND, met the inclusion criteria. Identified comparator trials included interferon β-1a (Rebif® and Avonex®), interferon β-1b (Betaferon®) and natalizumab.
- Differences in populations and outcomes, and imbalances in treatment effect modifiers, meant assumptions of similarity and homogeneity required for a network meta-analysis (NMA) approach were not met.
- The availability of patient-level data for the EXPAND trial allowed individual comparisons to each of the SPMS trials identified, using a matching-adjusted indirect comparison (MAIC) approach. However, this was only deemed feasible for the ITT population and not for the Active SPMS subgroup population.
- HRs between siponimod and the comparator ranged from [redacted] for 3-month CDP and [redacted] for 6-month CDP.
- ARR ratios between siponimod and the comparator range from [redacted] ([redacted]).

The results demonstrated siponimod to be tolerable, with an acceptable adverse event (AE) profile

- The most frequent TEAEs (>10% patients) in the siponimod arm of the trial were headache ([redacted]%), nasopharyngitis ([redacted]%), urinary tract infection ([redacted]%) and fall ([redacted]%).

- No difference in the rate of deaths or malignancies between siponimod and placebo was observed.

Siponimod is the first and only DMT to delay disability progression and cognitive impairment in a population which is representative of patients with SPMS.

- Due to the current lack of treatment options available for patients with SPMS, there is a strong clinical rationale for neurologists to avoid identifying SPMS in any patient currently receiving a DMT.
- Introduction of siponimod could create a step-change in identification of the transition to and management of SPMS in the NHS, by reducing the hesitancy of formally identifying SPMS.

B.2.1 *Identification and selection of relevant studies*

An SLR was conducted to identify relevant clinical evidence describing the effectiveness, safety and tolerability of pharmacological treatments for patients with SPMS. Full details of the SLR search strategy, study selection process, and results can be found in Appendix D.

B.2.2 *List of relevant clinical effectiveness evidence*

The SLR identified one RCT (EXPAND) for siponimod in SPMS for which published literature of the results was available. The results of the EXPAND trial, including data for the patient-reported HRQoL outcomes, are presented from the publication from Kappos *et al*.,[3] the interim clinical study report (CSR)[63] and CSR amendment.[64] A summary of the clinical effectiveness evidence from EXPAND is presented in Table 3.

Table 3: Clinical effectiveness evidence for siponimod in SPMS

Study	**EXPAND (NCT01665144)**		
Study design	Phase III, multicentre, randomised, double-blind, parallel-group, placebo-controlled trial		
Population	Patients with SPMS		
Intervention(s)	Siponimod 2 mg, taken daily		
Comparator(s)	Placebo, taken daily		
Indicate if trial supports application for marketing authorisation	Yes	**Indicate if trial used in the economic model**	Yes
Rationale for use/non-use in the model	EXPAND is the pivotal phase III trial for siponimod in patients with SPMS. This trial informed the marketing authorisation application and considers a population directly relevant to the decision problem addressed in the submission		
Reported outcomes specified in the decision problem	Primary Outcome Percentage of participants with **3-month CDP** events as measured by the EDSS. CDP was defined as a 1-point increase in EDSS if the baseline score was 3.0–5.0 or a 0.5 increase if the baseline score was 5.5–6.5 Secondary Outcomes *Key secondary objectives:* • Time to 3-month confirmed worsening of at least 20% from baseline in T25FW • Change from baseline in T2 lesion volume *Additional secondary objectives:*		

	• **Time to 6-month CDP as measured by the EDSS** • Reducing frequency of confirmed relapses: o **ARR** o Time to first relapse o Proportion of relapse-free patients • Patient-reported MSWS-12 • Inflammatory disease activity and burden of disease as measured by MRI: o Number of new or enlarging T2 lesions o Number of gadolinium-enhancing T1 lesions o Percentage change in brain volume from baseline • 3-month CDP in predefined sub-groups: o Patients with SPMS with or without superimposed relapses o Rapidly evolving patients, defined as 1.5 point or greater EDSS change in two years prior to study start o Patients with moderate and severe disease course, as defined by MSSS of four or more at baseline • HRQoL: o **EQ-5D** o MSIS-29 • Cognitive tests: o PASAT o SDMT o BVMT-R • Exploratory analysis: o MSFC o LCVA Safety Measures • TEAEs of treatment
All other reported outcomes	• Safety measures • Concomitant therapies

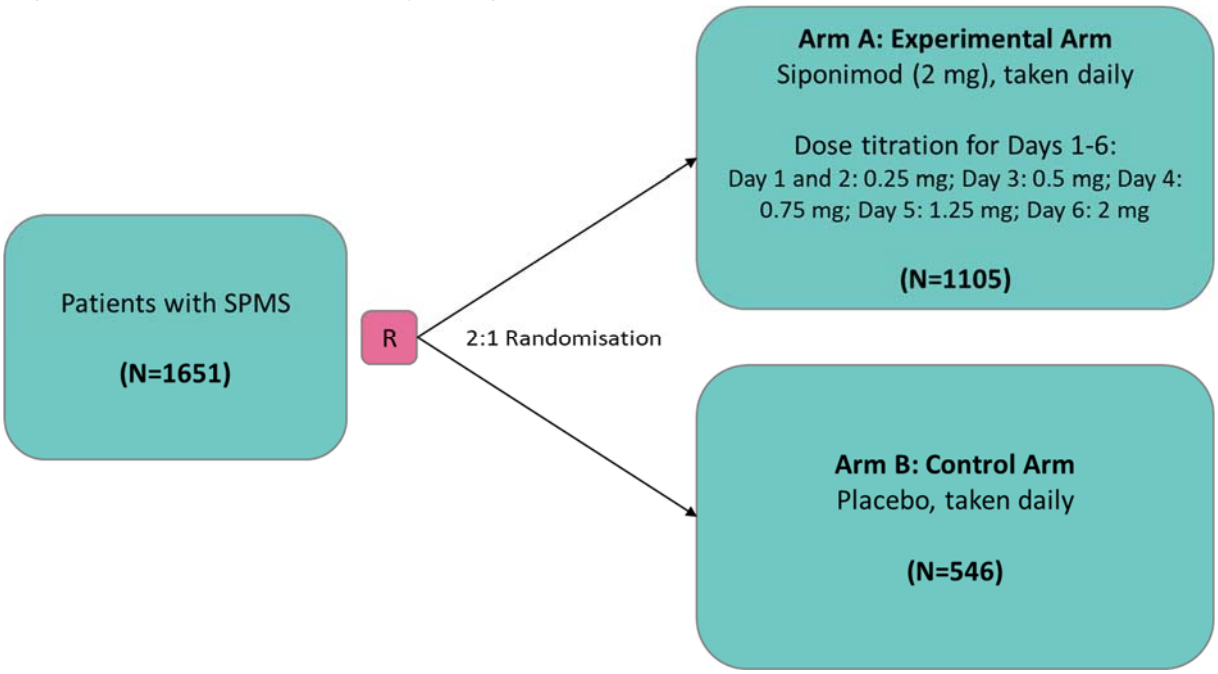
Outcomes in **bold** indicate those used in the economic model.
Abbreviations: ARR: annualised relapse rate; BVMT-R: brief visuospatial memory test revised; CDP: confirmed disability progression; EDSS: Expanded Disability Status Scale; HRQoL: health-related equality of life; LCVA: low-contrast visual acuity; MRI: magnetic resonance imaging; MSFC: multiple sclerosis functional composite; MSIS-29: multiple sclerosis impact scale; MSSS: multiple sclerosis severity scale; MSWS-12: 12-item multiple sclerosis walking scale; PASAT: paced auditory serial addition test; SDMT: symbol digit modalities test; SPMS: secondary progressive multiple sclerosis; TEAE: treatment emergent adverse effect; T25FW: timed 25-foot walk test.
Source: Kappos et al. 2018;[3] Novartis Data on File (Interim Clinical Study Report), 2014.[63]

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

B.2.3.1 Trial design

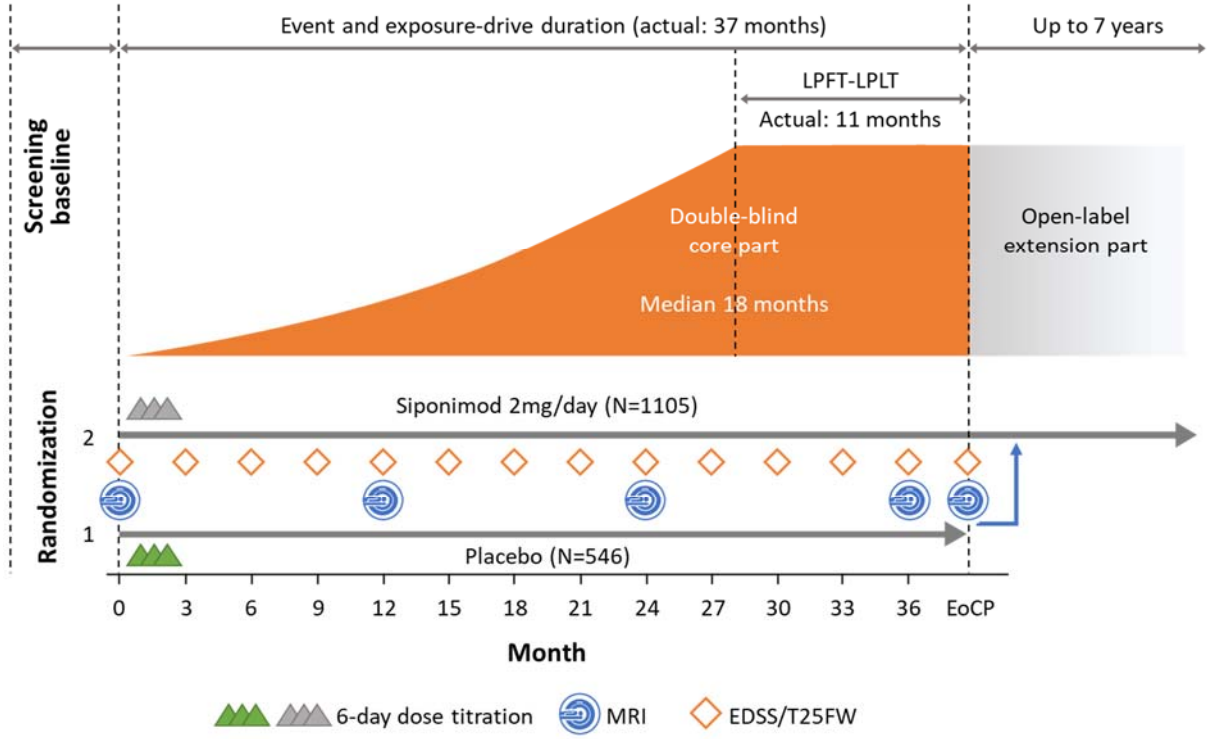
An overview of the study design is presented in Figure 3 and Figure 4.

Figure 3: Overview of the study design for EXPAND



Abbreviations: SPMS: secondary progressive multiple sclerosis.
Source: Kappos et al. 2018.[3]

Figure 4: Study design and recruitment for EXPAND



The y-axis of the graph indicates the enrolment of patients. Dark grey indicates the recruitment and double-blind core part. Light grey indicates the open-label extension phase. From Feb 5, 2013 to June 2, 2015, 1,651 patients were randomised to the core part at 292 sites in 31 countries.
Abbreviations: EDSS: Expanded Disability Status Scale; EoCP: end of core part; LPFT: last patient first treatment; LPLT: last patient last treatment; MRI: magnetic resonance imaging; T25FW: timed 25-foot walk.
Source: Kappos et al. 2018.[3]

B.2.3.2 Eligibility criteria

The key eligibility criteria for EXPAND are presented in Table 4. The full eligibility criteria can be found in Appendix L.

Table 4: Key eligibility criteria for EXPAND

Inclusion criteria	Exclusion criteria
• Ages 18–60 years • Diagnosis of SPMS • Documented moderate-to-advanced disability indicated by an EDSS score of 3.0–6.5 at screening • History of RRMS (2010 McDonald criteria)[67] • Documented EDSS progression in the 2 years before the study • No evidence of relapse or corticosteroid treatment in the 3 months before randomisation	• Substantial immunological, cardiac, or pulmonary conditions • Ongoing macular oedema • Uncontrolled diabetes • CYP2C9*3/*3 genotype • Varicella zoster virus antibody negative status

Abbreviations: CYP2C9: cytochrome P450 2C9; EDSS: Expanded Disability Status Scale; RRMS: relapsing-remitting multiple sclerosis; SPMS: secondary progressive multiple sclerosis.
Source: Kappos et al. 2018;[3] Novartis Data on File (Interim Clinical Study Report), 2014.[63]

B.2.3.3 Summary of EXPAND methodology

A summary of the methodology of EXPAND is available in Table 5.

Table 5. Summary of EXPAND methodology

Location	Multicentre
Trial Design	• Randomised, double-blind, parallel-group, placebo-controlled phase III study • Eligible patients were randomised 2:1 via Interactive Response Technology to receive siponimod or placebo • Randomisation was stratified by region • Patients with 6-month CDP during double-blind treatment were reconsented to either continue double-blind treatment, switch to open-label siponimod, or stop study treatment while following an abbreviated schedule of assessments and either remain untreated or receive another DMT • Patients, investigator staff, persons performing the assessments, and data analysts remained blinded to the identity of the treatment from the time of randomisation until database lock of the Core Part. Only Data Monitoring Committee members, independent statisticians, independent programmers and PK analysts (who kept PK results confidential until database lock) had access to the randomisation codes. Two separate databases were set up for the main data and the dose initiation data to preserve the blind.
Eligibility criteria for participants	People with SPMS The full inclusion and exclusion criteria are presented in Table 4 and Appendix L.
Settings and locations where the data were collected	International (314 study locations in 31 countries): Argentina, Australia, Austria, Belgium, Bulgaria, Canada, China, Czechia, Estonia, France, Germany, Greece, Hungary, Ireland, Israel, Italy, Japan, Latvia, Lithuania, Netherlands, Poland, Portugal, Romania, Russian Federation, Slovakia, Spain, Sweden, Switzerland, Turkey, United Kingdom (10 locations), United States
Trial drugs	• Siponimod arm (n=1,105): Siponimod 2 mg once daily. For Days 1–6, the dose was titrated from 0.25 mg to the 2 mg maintenance dose o Dose regimen: Day 1 and 2: 0.25 mg; Day 3: 0.5 mg; Day 4: 0.75 mg; Day 5: 1.25 mg o If treatment was interrupted for four or more consecutive days, re-titration was recommended • Placebo arm (n=546): Placebo once daily • The dose of 2 mg was based on the results of study A2201, a phase II dose-finding study of siponimod in patients with RRMS that investigated doses ranging from 0.25 mg to 10 mg. The MRI dose-response curve indicated near-maximal efficacy for the 2 mg dose • All drugs were administered orally

	• Patients with confirmed lymphocyte counts (at two consecutive visits, one week apart) of <0.2 x10^9/L, the dose was reduced to 1 mg per day in a blinded fashion o After a blinded dose reduction was implemented, the patient maintained the lower dose regardless of any increase in lymphocyte counts. Each patient was allowed only one dose change during double-blind treatment in the study • Patients who discontinued study treatment in the Core Part were asked to continue study participation according to an abbreviated visit schedule, following completion of an end of trial visit

Permitted and disallowed concomitant medication	• Patients were instructed to notify the study site about any new medications after enrolment into the study
	  o Recording of all medications and significant non-drug therapies (including physical therapy and blood transfusions) administered after enrolment in the study was required
	• Starting treatment with QT-prolonging or heart rate-lowering medications during study treatment initiation was to be avoided whenever possible. For patients receiving a stable dose of beta-blocker, resting heart rate was considered before starting study drug:
	  o If resting heart rate was >50 bpm under chronic beta-blocker treatment, study drug could be introduced
	  o If resting heart rate was ≤50 bpm, study treatment was not to be initiated. Beta-blocker treatment could be interrupted: once resting heart rate was >50 bpm, study drug could be initiated and after 2 weeks of treatment with study drug, beta-blocker treatment could be re-initiated
	• Introduction of beta-blocker treatment was allowed in patients who were receiving a maintenance dose of study treatment
	• Patients who were being treated with a stable dose of (dal)fampridine prior to enrolment in the study were allowed to enrol in the trial. However, patients were not to change or start treatment with (dal)fampridine while on double-blind study drug; with the exception of discontinuing (dal)fampridine due to unmanageable AEs
	• The administration of any live or live-attenuated vaccine (including for measles) was prohibited while patients were receiving study drug and for 1 week after study drug discontinuation. Administration of vaccines was permitted thereafter upon confirmation that lymphocyte levels were in the normal range

	Prohibited therapies
	• Class I: immunosuppressive/chemotherapeutic medications or procedures, including cyclosporine, azathioprine, methotrexate, cyclophosphamide, mitoxantrone, lymphoid irradiation and haematopoietic stem cell transplantation
	  o Discontinuation or interruption of study treatment, increased vigilance regarding infections
	  o Restarting study treatment was to first be discussed with the Novartis Medical Advisor

	• Class 2: Monoclonal antibodies targeting the immune system, including natalizumab, rituximab, ofatumumab, ocrelizumab and alemtuzumab o Discontinuation or interruption of study treatment, increased vigilance regarding infections o Restarting study treatment was to first be discussed with the Novartis Medical Advisor • Class 3: Any other immunomodulatory or disease-modifying MS treatment including, but not limited to: fingolimod, interferon β, glatiramer acetate or systemic corticosteroids (except when given for MS relapse treatment) o Interruption of study treatment, increased vigilance regarding infections • Class 4: Any concomitant medication that inhibits cardiac conduction (e.g., verapamil-type and diltiazem-type calcium channel blockers or cardiac glycosides) o Assessment of ECG and clinical status • Class 5: Potent inducers of CYP2C9
Primary outcomes	The pre-specified primary objective of this study was to demonstrate the efficacy of siponimod relative to placebo in delaying the time to 3-month CDP in patients with SPMS as measured by the EDSS • EDSS was assessed, based on neurological examination, by the Independent EDSS Rater every 3 months and in the case of a suspected MS relapse o EDSS uses an ordinal scale to assess neurological impairment in MS based on a neurological examination. Scores in each of seven functional systems (visual, brain stem, pyramidal, cerebellar, sensory, bowel and bladder, and cerebral) and an ambulation score were combined to determine the EDSS steps, ranging from 0 (normal) to 10 (death due to MS) • Disability progression was defined as an increased from baseline (Day 1) of: o 1 point in patients with a baseline EDSS score of 3.0 to 5.0, or o 0.5 point in patients with a baseline EDSS score of 5.5 to 6.5 • Sustained disability progression for 3-month CDP was determined by confirming that the criteria were also met at visits 3 months later, with any intervening EDSS values also meeting the criteria for change. EDSS scores used for confirmation of disability progression were to be obtained outside any ongoing relapse (the maximum duration of a relapse was defined as 90 days) • The Neurostatus eScoring system was used to capture EDSS data in this study in order to reduce variability and calculation errors and to improve data quality.

Other outcomes used in the economic model/specified in the scope	All efficacy and safety, and PROs, were pre-specified. Measures written in *italics* indicate key secondary variables (key as defined within the EXPAND trial) Efficacy • *Time to 6-month CDP as measured by the EDSS* • Multiple Sclerosis Functional Composite (MSFC) o Composite measure that assesses ambulation, upper extremity function, and cognitive function o The three components of the MSFC were assessed in this study by the Independent EDSS Rater or by another qualified individual every 3 months (T25FW and 9-HPT) or every 6 months (PASAT) o T25FW: measures the time, in seconds, to walk 25 feet (7.62 meters) o 9-HPT: assess upper extremity function by measuring the time, in seconds, required to insert and remove nine pegs. Measured for each arm separately o PASAT: measure of cognitive function that assesses auditory information processing speed and flexibility, as well as calculation ability • *Time to 3-month confirmed worsening of at least 20% from baseline in T25FW* • MS relapse analysis, including ARR (all relapses and confirmed relapses); time to first relapse; and proportion of patients free of relapses o MS relapse was defined as appearance of a new neurological abnormality or worsening of previously stable or improving pre-existing neurological abnormality, separated by at least 30 days from onset of a preceding clinical demyelinating event.[67] Additionally, the abnormality must have been present for at least 24 hours and occurred in the absence of fever (<37.5°C) or known infection o A confirmed MS relapse was defined as accompanied by a clinically-relevant change in the EDSS performed by the Independent EDSS Rater o ARR was defined as the average number of relapses per year and was analysed using a negative binomial regression model • MRI analysis o MRI scans of the brain were performed every 12 months o MRI evaluation during the Core Part, evaluated as compared to baseline, included, but was not limited to: ▪ *Total volume of T2 lesions* ▪ Number of new/enlarging T2 hyperintense lesions ▪ Number of T1 Gd-enhancing lesions ▪ Volume of T1 hypointense lesions ▪ Percentage change in brain volume

	▪ Number of new T1 hypointense lesions ▪ Number of new T1 hypointense lesions that were previously T1 Gd-enhancing lesions • Symbol digit modalities test (SDMT) o Assessed by Independent EDSS Rater or another qualified individual every six months o Assesses attention, concentration and processing speed: patients were presented with a test instrument that included a row of nine numbers paired with unique symbols at the top and an array of symbols paired with empty spaces below. The patient was required to verbally match the number with each symbol as rapidly as possible. The scoring was calculated based on the number of correct answers • Brief visuospatial memory test-revised (BVMT-R) o Assessed by Independent EDSS Rater or another qualified individual every six months o Measure of visuospatial memory used to document changes over time: during each of three consecutive learning tests, patients were shown the same sheet of geometric designs for 10 seconds following which they were instructed to draw the designs and the locations where the designs were seen, as accurately as possible. A delayed recall trial was administered after a 25-minute delay o Six different versions of the scale were used at alternating visits • Low contrast visual acuity (LCVA) o Assessed by Independent EDSS Rater or another qualified individual every six months o The 2.5% contrast chart was used for this study and consisted of rows of grey letters, decreasing in size from the top to the bottom row, on a white background. Standardised conditions were to be used (e.g. distance from the chart, lighting conditions) and the letter scores indicated the number of letters identified correctly. <u>Safety</u> • Safety assessments consisted of collecting all AEs, SAEs, with their severity and relationship to study drug, and pregnancies. • Regular monitoring of haematology, blood chemistry, and urine was performed by a central laboratory • Other safety assessments included: vital signs, physical examination, and body weight. Periodic routine 12-lead ECG, mobile cardiac telemetry (captures 24 hours heart rate and rhythm variations, however no ECG morphology or intervals, method was initially developed to capture rare episodes of rhythm disorder) or Holter monitoring (12-lead ambulatory 24-hour ECG method, which captures continuous data), pulmonary function tests and chest HRCT, ophthalmologic examination, and dermatological examinations were also performed <u>PROs</u>

	• The MSWS-12, MSIS-29 and EQ-5D-3L were included in this study • Patients completed the questionnaires prior to clinical assessments. Investigators reviewed the completed questionnaires before the clinical examination to identify any responses that might have indicated potential AEs or SAEs • Multiple sclerosis walking scale (MSWS-12) o Patient-rated measure of walking consisting of 12 items[68, 69] o Walking limitations were reported by the patients using categories (3 items had 3 response categories and 9 items had 5 response categories), generating a total transformed score ranging from 0−100. o Higher scores reflected greater impairment • Multiple sclerosis impact scale (MSIS-29) o 29-item, self-administered questionnaire that includes two domains: physical and psychological.[70] o Responses were captured on a 4-point ordinal scale ranging from 1 (not at all) to 4 (extremely), with higher scores reflecting greater impact on day-to-day life. The questions asked for the patient's views about the impact of MS on their day-to-day life during the prior 2 weeks • EQ-5D-3L
Pre-planned subgroups	Subgroup analyses were performed to examine whether the treatment difference was consistent in patients with different demographic/baseline or post-treatment disease characteristics. The following subgroups of patients were defined before the trial commenced: • Baseline demographic factors and treatment history (gender, previous interferon β-1b treatment, previous MS DMT treatment, [Previous IFNβ was added as a post-hoc analysis]) • Baseline disease characteristics: o Patients with SPMS or without superimposed relapses in the 2 years prior to the screening visit o Rapidly evolving patients (defined based on historical EDSS scores i.e. with an EDSS change ≥1.5 in the 2 years prior to or at study start). All patients who were adjudicated for disability progression were not assigned to the rapidly evolving patient subgroup o Disease course: patients with Global MSSS ≥4 were included in the moderate/severe subgroup o Number of T1 Gd-enhancing lesions at baseline (0; ≥1) • Patients with or without at least one confirmed relapse at any time on or after Day 1

Abbreviations: 9-HPT: nine-hole peg test; AE: adverse event; ARR: annualised relapse rate; BVMT-R: brief visuospatial memory test-revised; CDP: confirmed disability progression; CYP2C9: cytochrome P450 2C9; DMT: disease-modifying therapy; ECG: electrocardiogram; EDSS: Expanded Disability Status Scale; EQ-5D-3L: European quality of life 5-dimensions, 3-levels; HRCT: high resolution computed tomography; IFN: interferon; LCVA: low contrast visual acuity; MRI: magnetic resonance imaging; MS: multiple sclerosis; MSFC: multiple sclerosis functional composite; MSIS-29: multiple sclerosis impact scale; MSSS: multiple sclerosis severity score; MSWS-12: multiple sclerosis walking scale; PASAT: paced auditory serial addition test; PK: pharmacokinetics; PRO: patient reported outcome; RRMS: relapsing-remitting multiple sclerosis; SAE: serious adverse event; SDMT: symbol digit modalities test; SPMS: secondary progressive multiple sclerosis; T25FW: timed 25-foot walk test.
Source: Kappos et al. 2018;[3] Novartis Data on File (Interim Clinical Study Report), 2014;[63] EXPAND Clinical Study Record (ClinicalTrials.gov).[71]

B.2.3.4 Baseline characteristics

The baseline characteristics of patients included in the EXPAND study are summarised in Table 6; the full table of baseline characteristics can be found in Appendix L. A total of 1,651 patients were randomised to siponimod (n=1,105) or placebo (n=546). Patient characteristics at baseline were well balanced between treatment groups. The patients had a mean age of 48 years and most patients were female (60.1%), reflective of the fact that MS is more common in women than men.[5]

The patient population enrolled was consistent with an SPMS patient population; moderately to severely disabled (median EDSS score of 6.0) and low inflammatory disease activity as reflected in the low proportion of patients with Gd-enhancing lesions at screening (75.6% had none) and low number of patients with relapses in the previous 2 years (63.9% had no relapses in that time, and 78.4% did not have relapses within the year prior to screening). On average, patients had MS for approximately 17 years since onset of first symptoms and for approximately 13 years since diagnosis and had converted to SPMS nearly 4 years prior to baseline (ranging from 0.1–24.2 years).

Prior DMT treatments were received by 1,292 patients (78.3%). The three most common prior treatments in each treatment group were [redacted], [redacted], and [redacted]. and [redacted].[63]

Table 6: Summary of EXPAND patient baseline characteristics

Demographic variable	Siponimod N=1,105	Placebo N=546
Age groups – n (%)		
18–40	188 (17)	103 (19)
>40	917 (83)	443 (81)
Age (years)		
Mean (SD)	48.0 (7.8)	48.1 (7.9)
Median	49.0	49.0
Min – Max	22–61	21–61
Sex – n (%)		
Female	669 (61)	323 (59)
Male	436 (39)	223 (41)
Duration of MS since diagnosis (years)		
Mean (SD)	12.9 (7.9)	12.1 (7.5)
Median	12.0	11.2
Min – Max	0.1–44.4	0.4–39.4
Duration of MS since first symptom (years)		
Mean (SD)	17.1 (8.4)	16.2 (8.2)
Median	16.4	15.4
Min – Max	1.4–45.0	1.3–43.0
Time since conversion to SPMS (years)		

Demographic variable	Siponimod N=1,105	Placebo N=546
Mean (SD)	3.9 (3.6)	3.6 (3.3)
Median	2.6	2.5
Min – Max	0.1–24.2	0.1–21.7
Number of relapses in the last 2 years prior to screening		
Mean (SD)	0.7 (1.2)	0.7 (1.2)
Median	0.0	0.0
Min – Max	0–12	0–8
Number of relapses in the last 2 years prior to screening (categories) – n (%)		
None	712 (64)	343 (63)
Number of relapses in the last year prior to screening		
Mean (SD)	0.2 (0.5)	0.3 (0.6)
Median	0.0	0.0
Min – Max	0–4	0–4
Number of relapses in the last year prior to screening (categories) – n (%)		
None	878 (79)	416 (76)
EDSS		
Mean (SD)	5.4 (1.1)	5.4 (1.0)
Median	6.00	6.00
Min – Max	2.0–7.0	2.5–7.0
EDSS (categories) – n (%)		
<3.0	6 (1)	2 (<1)
3.0–4.5	312 (28)	148 (27)
5.0–5.5	165 (15)	100 (18)
6.0–6.5	620 (56)	295 (54)
>6.5	2 (<1)	1 (<1)
Number of Gd-enhancing T1 lesions (categories) – n (%)		
0	833 (75)	415 (76)
≥1	237 (21)	114 (21)
Not assessed	35 (3)	17 (3)
Volume of T2 lesions (mm^3)		
Mean (SD)	15,632 (16,268)	14,694 (15,620)
Median	10,286	9,994
Min – Max	23–116,664	0–103,560
Normalised brain volume (cc)		
Mean (SD)	1,422 (86)	1,425 (88)
Median	1,421	1,425
Min – Max	1,136–1,723	1,199–1,691
MS DMTs (Approved for the treatment of MS)		
Any MS DMT	860 (78)	432 (79)
No previous use	245 (22)	114 (21)

Abbreviations: 9-HPT: nine-hole peg test; DMT: disease-modifying therapy; EDSS: Expanded Disability Status Scale; MS: multiple sclerosis; MSSS: multiple sclerosis severity scale; SD: standard deviation; SDMT: symbol digit modalities test; SPMS: secondary progressive multiple sclerosis; T25FW: timed 25-foot walk test
Source: Kappos et al. 2018.[3]

B.2.3.5 Concomitant medications

Most patients ([redacted]) took concomitant medications. Nervous system was the most common anatomical therapeutic chemical level 1 category in which patients took concomitant medications ([redacted] siponimod, [redacted] placebo), primarily other analgesics and antipyretics ([redacted] siponimod, [redacted] placebo), anti-depressants ([redacted] siponimod, [redacted] placebo), anti-epileptics ([redacted] siponimod, [redacted] placebo), and anxiolytics ([redacted] siponimod, [redacted] placebo).

Five classes of medications were defined as prohibited medications (Table 5). If these medications were taken concomitantly with study drug, these were considered as protocol deviations. The percentages of patients who took prohibited concomitant medications while receiving study drug were low within each of the five classes ([redacted]), and were similar between treatment groups.

Concomitant surgical and medical procedures were reported in [redacted] of siponimod patients and [redacted] of placebo patients. Physiotherapy was the most common preferred term ([redacted] of patients overall).

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

All efficacy analyses including the primary outcome of time to 3-month CDP were performed on the full analysis set (FAS) population. This comprised all randomised patients with assigned treatment who took at least one dose of study medication. Patients were analysed according to the randomised treatment assignment following the ITT principle, using all available efficacy assessments, irrespective of the study treatment received. Data for patients receiving open-label therapy are included in the analysis based on the original treatment group assignment.

All safety analyses were performed on the safety set population. This comprised all patients who received at least one dose of study medication. Patients were analysed according to the actual treatment received, using all available data up to and including 30 days after last dose of study drug or the day before the start of open-label siponimod, whichever came first.

By the end of the trial, [redacted] patients ([redacted]) in the siponimod arm and [redacted] patients ([redacted]) in the placebo arm had discontinued treatment. A full CONSORT diagram of the study population flow is provided in Appendix D.

The statistical analyses used for the primary endpoint, alongside the sample size calculations and methods for handling missing data are presented in Table 7.

Table 7. Summary of statistical analyses in EXPAND

Hypothesis objective	The study was designed to demonstrate superiority of siponimod to placebo with respect to 3-month CDP. The null and alternative hypotheses were defined as follows: • Null hypothesis (H0): tested that there was no difference in the time to 3-month CDP between the siponimod and placebo group

	• Alternative hypothesis (H1): there was a difference between the groups The null hypothesis was to be rejected if the observed p-value for the between-group comparison was less than a significance level (two sided) adjusted according to the O'Brien-Fleming alpha level correction[72] which was calculated to be 0.0434.
Statistical analysis	Primary Outcome: • The primary variable was time to 3-month CDP based on EDSS • Baseline EDSS was defined as the latest available EDSS assessment prior to or on Day 1 (day of first dose) • The criteria to reach the 3-month disability progression included detection of onset of progression and confirmation of progression • All available post-baseline EDSS scores (scheduled or unscheduled) were evaluated to assess if the change from baseline met the disability progression criterion. The first EDSS assessment that met the criterion defined the onset of tentative disability progression • Progression was confirmed if a subsequent scheduled visit at least 3 months (i.e. ≥76 days) after onset showed progression and every EDSS score (scheduled or unscheduled) obtained between the onset and confirmation visits also met the progression criterion. Only the EDSS assessments obtained at scheduled visits (including follow-up visits) and in the absence of relapse (confirmed or unconfirmed) were to be used for confirmation of progress • For patients with confirmed progression, the time to 3-month CDP was calculated from the date of Day 1 to the date of the CDP onset • The hypothesis was tested using a Cox proportional hazards model with treatment, country, baseline EDSS and SPMS group (with or without superimposed relapses at baseline) as covariate. • The estimated HR (siponimod/placebo hazard rates) with 95% Wald CI was obtained. The risk reduction in percent was calculated as (1 - HR) x 100. • Kaplan-Meier estimates (with 95% confidence intervals) were summarised at Month 12, Month 24, and Month 36. • In the Cox proportional hazards model, the assumption of proportionality of the hazard functions over time was made. The assumption was checked using a Cox proportional hazards model that included a treatment and a time-dependent explanatory variable created through the interaction between treatment and time. A graphical method (log-log survivor function vs time) was used for checking the proportional hazards assumption. Approximate parallelism between the curves for the treatment groups would provide supportive evidence of the proportional hazards assumption.
Sample size, power calculation	• The study was designed to have 90% power to detect a 30% reduction in the risk of 3-month CDP (HR of 0.70), using a log-rank test with 2-sided alpha level of 5% and 2:1 randomisation of siponimod to placebo • Assuming a 2-year proportion with disability progression of 0.30 in the placebo group, a 2-year drop-out rate of 20%, and an enrolment rate of 100 patients per month, 1,530 patients and an overall study duration of approximately 42 months were required to observe at least 374 patients with disability progression, which would give the required power. In this calculation, exponential distribution assumptions were used for the event and drop-out rates

	• The protocol was amended to update the criterion for stopping the Core Part of the study from 374 patients with 3-month CDP had been observed (original plan) to approximately 3 years after randomisation of the first patient and at least 374 events observed. At approximately 3 years, it was expected that more than 374 patients with 3-month CDP had been observed. This was expected to compensate for the slight power loss due to the alpha adjustment for the interim analysis and a power of at least 90% was expected at the end of the Core Part
Data management, patient withdrawals	The primary analysis of the time to 3-month CDP used all available data from all patients in the FAS, irrespective of premature discontinuation from study medication.

Abbreviations: CDP: confirmed disability progression; CI: confidence interval; EDSS: Expanded Disability Status Scale; FAS: full analysis set; H0: null hypothesis; H1: alternative hypothesis; HR: hazard ratio; SPMS: secondary progressive multiple sclerosis.
Source: Novartis Data on File (Interim Clinical Study Report), 2014.[63]

B.2.5 *Quality assessment of the relevant clinical effectiveness evidence*

Overall, the results of the EXPAND trial may be considered to be at low risk of bias. Randomisation, concealment of treatment allocation and blinding of the participants and care providers were adequate. Baseline characteristics were well balanced between the treatment groups at baseline. All randomised patients were included in the ITT analysis for primary and secondary efficacy outcomes. There was no difference in the rates of treatment discontinuation between treatment arms. A summary of the quality assessment for EXPAND is provided in Table 8. The full quality assessment can be found in Appendix D.

Table 8: Overview of quality assessment for EXPAND

	Risk of bias
Was randomisation carried out appropriately?	Low risk of bias
Was the concealment of treatment allocation adequate?	Low risk of bias
Were the groups similar at the outset of the study in terms of prognostic factors?	Low risk of bias
Were the care providers, participants and outcome assessors blind to treatment allocation?	Low risk of bias
Were there any unexpected imbalances in drop-outs between groups?	Low risk of bias
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Low risk of bias
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Low risk of bias

Adapted from Systematic Reviews: CRD's guidance for undertaking reviews in health care (University of York Centre for Reviews and Dissemination).

B.2.6 *Clinical effectiveness results of the relevant trials*

The EXPAND study met its primary endpoint, demonstrating a statistically significant and clinically meaningful improvement in delaying the time to 3-month CDP as measured by EDSS.

- By delaying disability progression, patients are able to maintain their current level of physical and cognitive abilities and their quality of life for longer, for instance by extending the time prior to a patient requiring permanent use of a wheelchair.
- Siponimod displayed a 21.2% risk reduction compared with placebo for time to 3-month CDP (HR 0.79, p=0.0134). Kaplan-Meier estimates indicated that the time to first quartile (25%) of patients experiencing 3-month CDP events was observed approximately 6 months later in patients randomised to siponimod relative to patients randomised to placebo.
- Siponimod treatment also delayed the time to 6-month CDP compared with placebo with a risk reduction of 25.9% (HR 0.74, p=0.0058, unadjusted for multiplicity).
- Delaying the time to 3-month confirmed worsening in T25FW of at least 20% from baseline showed a risk reduction of 6.2% in favour of siponimod, but this did not reach statistical significance. However, T25FW is thought to have suboptimal sensitivity for change in patients with more advanced MS, such as those in the EXPAND trial. Improvement in MSWS-12 also did not reach statistical significance.
- Siponimod displayed improvement in patients compared with placebo across all MRI outcomes measured: smaller increase in T2 lesion volume; fewer Gd-enhancing T1 lesions; fewer new or newly enlarging T2 lesions; and a smaller decrease in brain volume.
- An improvement in patients taking siponimod compared with placebo was also seen across all relapse-related measures: 55.5% rate reduction for confirmed relapses; delayed time to first relapse; and fewer patients experienced relapses. Combined with the improvements in MRI activity, this demonstrates a reduction in inflammatory activity in these patients.
- [redacted] in HRQoL measures were observed for both the physical MSIS-29 and EQ-5D utility scores at Month 12, but these were [redacted] to Month 24, however the apparently [redacted] between-group differences at Month 24 compared with Month 12 should be interpreted in light of the small sample size and higher variability at Month 24 due to the event-driven trial design.
- Siponimod showed a [redacted] compared with placebo for the cognitive measure of SDMT at Month 12, which [redacted] at Month 24, showing [redacted] deterioration in attention, concentration and processing speed.
- Sensitivity analyses to explore the effect of siponimod on CDP, unrelated to the effect on relapses, gave results consistent with the effect on overall population for 3-month CDP (RR [redacted] vs HR 0.79) and 6-month CDP (RR [redacted] vs HR 0.74).[65]
- From the results of the ongoing extension phase of the EXPAND trial, siponimod showed evidence of maintained treatment effect with respect to 6-month CDP after 5.5 years (RPSFT-adjusted HR [redacted] compared with 0.74 at the end of the core part of the trial).[66]
- Overall, the results of the EXPAND trial clearly demonstrate the clinical efficacy of siponimod in patients with SPMS, with a meaningful delay in disability progression, both in terms of EDSS progression, and MRI and relapse activity.

B.2.6.1 Confirmed disability progression

Siponimod demonstrated a 21.2% risk reduction compared with placebo for time to 3-month CDP based on EDSS and a 25.9% risk reduction for time to 6-month CDP, resulting in a meaningful delay in disability progression for patients with SPMS. By delaying disability progression, patients are able to maintain their current level of physical and cognitive abilities

and their quality of life for longer, for instance by extending the time prior to a patient requiring permanent use of a wheelchair.

Time to 3-month CDP

The primary efficacy objective was to compare siponimod versus placebo in delaying the time to 3-month CDP in patients with SPMS as measured by the EDSS. A 3-month CDP required that the EDSS score at progression, the 3-month confirmatory EDSS score and any EDSS scores obtained in between met the disability progression criteria. The confirmatory EDSS score could not have been recorded during an MS relapse.

Siponimod showed a 21.2% risk reduction compared with placebo for time to 3-month CDP based on EDSS that was statistically significant (Table 9, HR 0.79, p=0.0134).

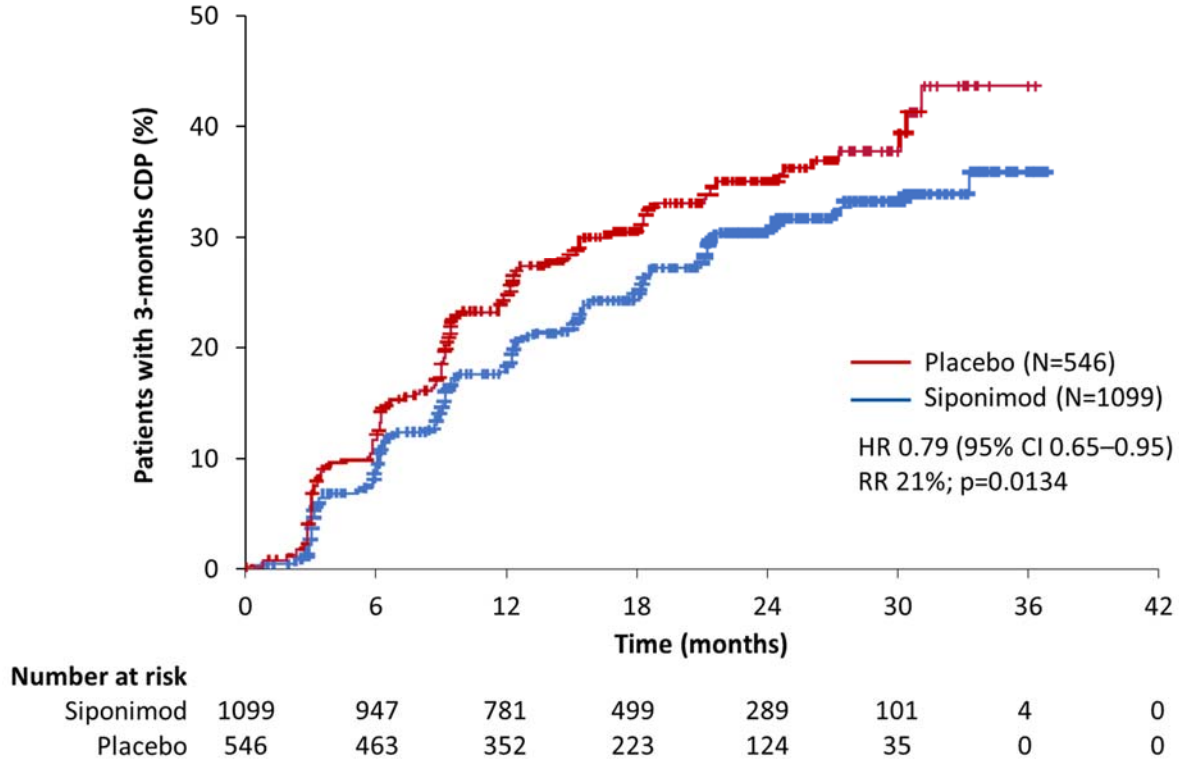
Kaplan-Meier estimates for the percentage of patients free of 3-month CDP events were provided at Months 12, 24, and 36. Kaplan-Meier curves showed difference between siponimod and placebo, in favour of siponimod. Separation started early and was sustained over time (Figure 5; Appendix L). The log-rank test was statistically significant, indicating a delay in time to 3-month CDP in the siponimod group (p=0.0129). Kaplan-Meier estimates indicated that the time to first quartile (25%) of patients experiencing 3-month CDP events was observed approximately 6 months later in patients randomised to siponimod relative to patients randomised to placebo.

Table 9: Time to 3-month CDP based on EDSS – Cox proportional hazards model

Treatment	n/N'	%	Comparison: Siponimod vs Placebo*		
			Risk reduction	HR (95% CI)	p-value
Siponimod (N=1,099)	288/1,096	26.3	21.2%	0.79 (0.65; 0.95)	0.0134
Placebo (N=546)	173/545	31.7			

n/N': n= number of subjects with events/N'=number of subjects included in the analysis (i.e. with non-missing covariates).
*Using a Cox proportional hazards model with treatment, country/region, baseline EDSS, and SPMS group (with/without superimposed relapses, baseline definition) as covariates. Risk reduction is derived as (1-HR) * 100. For three siponimod patients and one placebo patient, information on the number of relapses in the last 2 years could not be derived (missing).
Abbreviations: CDP: confirmed disability progression; CI: confidence interval; EDSS: Expanded Disability Status Scale; HR: hazard ratio; SPMS: secondary progressive multiple sclerosis.
Source: Kappos et al. 2018.[3]

Figure 5: Time to 3-month CDP based on EDSS – Kaplan-Meier curves



Number at risk								
Siponimod	1099	947	781	499	289	101	4	0
Placebo	546	463	352	223	124	35	0	0

Abbreviations: CDP: confirmed disability progression; CI: confidence interval; EDSS: Expanded Disability Status Scale; HR: hazard ratio; RR: risk ratio.
Source: Kappos et al. 2018.[3]

The time to 3-month CDP being sustained until last observation was analysed using the Cox proportional hazards model. This showed a risk reduction of [redacted] for siponimod relative to placebo, which was [redacted]. This is graphically depicted using Kaplan-Meier curves (Figure 6).

Figure 6: Patients free of 3-month CDP based on EDSS and sustained until the end of the Core Part – Kaplan-Meier curves

[redacted]

Abbreviations: CDP: confirmed disability progression; EDSS: Expanded Disability Status Scale.
Source: Novartis Data on File (Clinical Study Report for Siponimod).[63]

Time to 6-month CDP

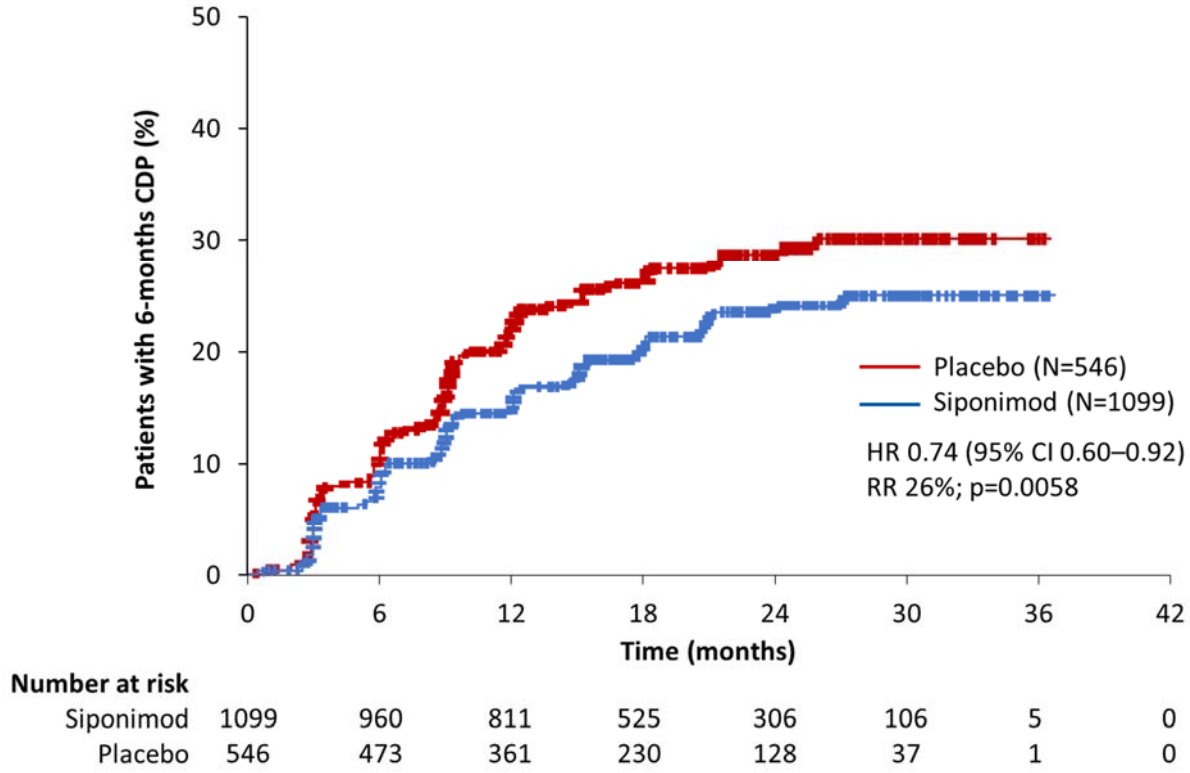
Siponimod treatment delayed the time to 6-month CDP compared with placebo (Table 10). Risk reduction of 25.9% in 6-month CDP was observed for siponimod compared with placebo (HR 0.74, p=0.0058, unadjusted for multiplicity). Kaplan-Meier curves (Figure 7; Appendix L) represent the same results.

Table 10: Time to 6-month CDP based on EDSS – Cox proportional hazards model

Treatment	n/N'	%	Comparison: Siponimod vs Placebo*		
			Risk reduction	HR (95% CI)	p-value
Siponimod (N=1,099)	218/1,096	19.9	25.9%	0.74 (0.60; 0.92)	0.0058
Placebo (N=546)	139/545	25.5			

n/N': n= number of subjects with events/N'=number of subjects included in the analysis (i.e. with non-missing covariates)
*Using a Cox proportional hazards model with treatment, country/region, baseline EDSS, and SPMS group (with/without superimposed relapses, baseline definition) as covariates. Risk reduction is derived as (1-HR) * 100
Abbreviations: CDP: confirmed disability progression; CI: confidence interval; EDSS: Enhanced Disability Status Scale; HR: hazard ratio; SPMS: secondary progressive multiple sclerosis.
Source: Kappos et al. 2018.[3]

Figure 7: Time to 6-month CDP based on EDSS – Kaplan-Meier curves



Abbreviations: CDP: confirmed disability progression; CI: confidence interval; EDSS: Expanded Disability Status Scale; HR: hazard ratio; RR: risk ratio.
Source: Kappos et al. 2018.[3]

Time to 6-month CDP sustained until last observation in the core part was analysed using the Cox proportional hazards mode. The results were supportive of the results obtained for the main

analysis, showing a risk reduction of [redacted] for siponimod relative to placebo [redacted].

B.2.6.2 Functional measures

Both functional measures T25FW and MSWS-12 showed improvements in patients' ability to walk but these improvements did not reach statistical significance. However, it is thought that T25FW may have suboptimal sensitivity for change in patients with advanced MS, such as those in the EXPAND trial. [redacted] was observed in EXPAND for the T25FW test that becomes [redacted] in patients with higher baseline EDSS scores, limiting the ability to reliably detect changes and treatment effect in the T25FW test in patients with an EDSS [redacted] (median EDSS in EXPAND was 6.0).

Time to 3-month confirmed worsening in T25FW

The results for time to 3-month confirmed worsening in T25FW of at least 20% from baseline are summarised in Table 11. There was an observed risk reduction of 6.2% in favour of the siponimod group (p=0.4398).

Table 11: Proportion of patients reaching 3-month confirmed worsening in T25FW of at least 20% from baseline – Cox proportional hazards model

Treatment	n/N'	%	Comparison: Siponimod vs Placebo*		
			Risk reduction	HR (95% CI)	p-value
Siponimod (N=1,099)	432/1,087	39.7	6.2%	0.94 (0.80; 1.10)	0.4398
Placebo (N=546)	225/543	41.4			

n/N': n= number of subjects with events/N'=number of subjects included in the analysis (i.e. with non-missing covariates)
*Using a Cox proportional hazards model with treatment, country/region, baseline EDSS, baseline T25FW, and SPMS group (with/without superimposed relapses, baseline definition) as covariates.
Risk reduction is derived as (1-HR) * 100.
Abbreviations: CI: confidence interval; EDSS: Expanded Disability Status Scale; HR: hazard ratio; SPMS: secondary progressive multiple sclerosis; T25FW: timed 25-foot walk test.
Source: Kappos et al. 2018;[3] Novartis Data on File (Clinical Study Report for Siponimod).[63]

This secondary endpoint did not reach statistical significance. The T25FW test was included in the study as an additional walking-related endpoint in addition to the aspect of walking captured by the EDSS measure. However, studies documenting the T25FW test as a relevant and valid endpoint have been based mainly on fully ambulatory patients with RRMS and EDSS scores up to 5.5; more advanced patients with baseline EDSS scores of 6.0 or higher were typically excluded or underrepresented.[73, 74] A recent validation study in patients with progressive MS (mainly SPMS), published after the EXPAND trial commenced, found the T25FW test was poorly responsive in patients with moderate-to-severe disability (mean EDSS score of 6.0 or above).[75] It is thought that T25FW may have suboptimal sensitivity for change in patients with more advanced MS (such as those in the EXPAND trial, with mean EDSS 5.4 at baseline),[3] as small increases in the EDSS can substantially affect their mobility.

More than 50% of patients in the EXPAND trial had an EDSS 6.0 or higher at baseline. Figure 8 shows the [redacted] for the T25FW test

observed in EXPAND that becomes [redacted] in patients with higher baseline EDSS scores, which may have limited the ability to reliably detect changes and treatment effect in the T25FW test in patients with an EDSS [redacted].

Figure 8: T25FW at baseline by EDSS score

Abbreviations: EDSS: Expanded Disability Status Scale; T25FW: timed 25-foot walk test.

Additionally, nurses at a clinical advisory board organised by Novartis commented that the test may not be representative as it judges patients on just a single day, and it is not known how far the patient has already had to walk to the assessment centre. Patients often experience a high level of stress surrounding the test, which can lead to poor results. The reliability of this test is also affected by differences in test administration instructions (e.g. “static” vs “dynamic” start, “comfortable” vs “maximum, but safe” pace),[76] meaning it may not be the most appropriate measure for ambulatory performance.

Multiple Sclerosis Walking Scale (MSWS-12)

Change from baseline in MSWS-12 converted score is provided in Table 12: this is calculated by converting the MSWS-12 score to a 0 to 100 scale by subtracting the minimum score (12) from the patient’s MSWS-12 score, dividing my the maximum score minus the minimum score (48), and multiplying the result by 100. Total transformed scores on the MSWS-12 can range from 0-100 with higher scores reflecting greater impairment. The mean MSWS-12 score at baseline was [redacted], reflecting the high disability status of the population. More than [redacted] of the patients had a score higher than 72.9.

The difference in adjusted means in the siponimod group showed smaller increases from baseline compared with placebo at Month 12 and Month 24; however, the differences between groups were not statistically significant (the difference at Month 12 was nominally significant). The apparently smaller between-group differences at Month 24 compared with Month 12 should be interpreted in light of the smaller sample size and higher variability at Month 24. Additionally, given the high values at baseline, further increase could only be modest (ceiling effect) and there was not much room for a differentiation of siponimod from placebo in the change from baseline.

Table 12: Change from baseline in MSWS-12 converted score, by timepoint – repeated measures model

Time-point	Adjusted means (SE)		Comparison of adjusted means Siponimod vs Placebo			
	Siponimod (N'=1,022)	Placebo (N'=516)	Difference	SE	95% CI	p-value
Month 12	1.53 (0.678)	3.36 (0.908)	−1.83	1.030	(−3.85; 0.19)	0.0764
Month 24	4.16 (0.848)	5.38 (1.167)	−1.23	1.359	(−3.89; 1.44)	0.3671

N'=number of subjects included in the analysis (i.e. with a baseline and at least one post-baseline MSWS-12 converted score).
Obtained from fitting a repeated measures model (assumes normally distributed data) with visit as categorical factor. Model was adjusted for treatment, region/country, baseline MSWS-12 converted score. Adjusted means refers to the change from baseline in MSWS-12.
Abbreviations: CI: confidence interval; MSWS-12: multiple sclerosis walking scale; SE: standard error.
Source: Kappos et al. 2018;[3] Novartis Data on File (Clinical Study Report for Siponimod).[63]

B.2.6.3 MRI activity

Siponimod displayed improvement in patients compared with placebo across all MRI measures: smaller increase in T2 lesion volume; fewer Gd-enhancing T1 lesions; fewer new or newly enlarging T2 lesions; and smaller decrease in brain volume.

T2 lesion volume

The results for change from baseline in T2 lesion volume at Month 12 and 24 are summarised in Table 13. The adjusted mean refers to the change from baseline in T2 lesion volume at each timepoint. For the change from baseline in T2 lesion volume at both Month 12 and Month 24, nominal p-values of <0.0001 were observed for between-treatment comparisons at both timepoints as well as for the average over Month 12 and Month 24.

Table 13: Change from baseline in T2 lesion volume (mm^3) by timepoint – repeated measures model

Time-point	Adjusted means (SE)		Comparison of adjusted means Siponimod vs Placebo			
	Siponimod (N'=995)	Placebo (N'=495)	Difference	SE	95% CI	p-value
Month 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Average over Months 12 and 24	183.9 (66.33)	879.2 (85.43)	−695.3	92.79	(−877.3; −513.3)	<0.0001

N'=number of subjects included in the analysis (i.e. with at least MRI scan post-baseline and non-missing covariates).
Obtained from fitting a repeated measures model (model assumes normally distributed data) with visit as a categorical factor. Model was adjusted for treatment, country/region, baseline T2 lesion volume, number of T1 Gd-enhancing lesions at baseline, SPMS group (with/without superimposed relapses, baseline definition). Adjusted mean refers to the change from baseline in T2 lesion volume.

Abbreviations: CI: confidence interval; MRI: magnetic resonance imaging; SE: standard error; SPMS: secondary progressive multiple sclerosis.
Source: Kappos et al. 2018;[3] Novartis Data on File (Clinical Study Report for Siponimod).[63]

The yearly change in T2 lesion volume was analysed using a random coefficients model. The yearly change estimate was [redacted] in the siponimod group compared with [redacted] in the placebo group, showing a difference between groups ([redacted]). These results demonstrate a reduction in T2 lesion volume in siponimod-treated patients compared with those receiving placebo. The limitation of this analysis was it assumes that change in T2 lesion from baseline is linear over time.

T1 Gd-enhancing lesions

The proportion of patients free of T1 Gd-enhancing lesions is summarised in Table 14. At baseline, approximately 75% of patients in each group did not have T1 Gd-enhancing lesions. Over all post-baseline scans, 89.4% of siponimod patients and 66.9% of placebo patients were free of T1 Gd-enhancing lesions.

The results for number of T1 Gd-enhancing lesions by timepoint are summarised in Table 15. The mean number of lesions per scan was low in each treatment group. Differences, favouring siponimod, were seen for number of T1 Gd-enhancing lesions at Month 12 and Month 24 ($p<0.0001$, unadjusted for multiplicity).

Table 14: Proportion of patients free of T1 Gd-enhancing lesions, by timepoint – summary statistics

	Siponimod, N=1,099 n/m	Placebo, N=546 n/m
Proportion of patients free of T1 Gd-enhancing lesions (in this scan)		
Month 12	[redacted]	[redacted]
Month 24	[redacted]	[redacted]
Proportion of patients free of T1 Gd-enhancing lesions (all post-baseline scans)		
All post-baseline scans	917/1,026 (89.4)	341/510 (66.9)

n=number of subjects who are free of lesions.
For all post-baseline scans, m=number of subjects with at least one post-baseline result
At timepoints evaluated on a single MRI scan, m=number of subjects with result in this scan.
Source: Kappos et al. 2018;[3] Novartis Data on File (Clinical Study Report for Siponimod).[63]

Table 15: T1 Gd-enhancing lesions per patient per scan, by timepoint – repeated measures negative binomial regression

Time-point	Adjusted mean (95% CI)*		Between-treatment comparison* Siponimod vs Placebo			
	Siponimod (N'=996)	Placebo (N'=496)	Rate reduction	Rate ratio	95% CI	p-value
Number of T1 Gd-enhancing lesions (in this scan)**						
Month 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cumulative number of T1 Gd-enhancing lesions (all post-baseline scans)						

All post-baseline scans	0.08 (0.07; 0.10)	0.60 (0.47; 0.76)	86.7%	0.14	0.10; 0.19	<0.0001

N'=number of patients included in the analysis (i.e. with at least one MRI scan post-baseline and non-missing values for the covariates included in the model).
Adjusted mean (or rate) refers to the adjusted number of lesions per subject per scan. Rate reduction is derived as (1- rate ratio) * 100.
*Obtained from fitting negative binomial regression model adjusted for treatment, age, baseline number of T1 Gd-enhancing lesions (offset=number of scheduled MRI scans).
**A repeated measures regression model was implemented with visit as a categorical factor.
Abbreviations: CI: confidence interval; MRI: magnetic resonance imaging.
Source: Kappos et al. 2018;[3] Novartis Data on File (Clinical Study Report for Siponimod).[63]

The number of Gd lesions at each timepoint and cumulative number of T1 Gd-enhancing lesions/per scan (i.e. total number of lesions observed over all timepoints divided by the total number of scans) were lower at each post-baseline timepoint in the siponimod group compared with the placebo group.

New or newly enlarging T2 lesions

A larger proportion of patients randomised to siponimod remained free of new or enlarging T2 lesions compared with placebo (Table 16). The proportions of patients free of new or enlarging T2 lesions compared with the previous scan were [redacted] and [redacted] for siponimod and [redacted] and [redacted] for placebo patients at Months 12 and 24, respectively. For all post-baseline scans (performed annually), 56.9% of siponimod patients and 37.3% of placebo patients were free of new or enlarging T2 lesions.

The results for number of new or enlarging T2 lesions by timepoint are summarised in Table 17. The rate ratio was the ratio of adjusted mean number of new/enlarging T2 lesions for siponimod versus placebo and rate reduction was derived from rate ratio. The mean number of new/enlarging T2 lesions compared with the previous scan favoured siponimod over placebo at Month 12 ([redacted] rate reduction) and Month 24 ([redacted], p<0.0001, unadjusted for multiplicity), showing fewer patients with new/enlarging T2 lesions relative to placebo.

Table 16: Proportion of patients free of new or enlarging T2 lesions, by timepoint – summary statistics

	Siponimod, N=1,099 n/m	Placebo, N=546 n/m
Proportion of patients free of new or enlarging T2 lesions (in this scan relative to previous scan)		
Month 12	[redacted]	[redacted]
Month 24	[redacted]	[redacted]
Proportion of patients free of new or enlarging T2 lesions (overall)		
All post-baseline scans	584/1,026 (56.9)	190/510 (37.3)

n=number of subjects who are free of lesions.
At last assessment timepoints, m=number of subjects at least one post-baseline result
At timepoints evaluated on a single MRI scan, m=number of subjects with result in this scan.
Source: Kappos et al. 2018;[3] Novartis Data on File (Clinical Study Report for Siponimod).[63]

Table 17: New or enlarging T2 lesions, by timepoint – repeated measures negative binomial regression

Time-point	Adjusted mean (95% CI)*	Between-treatment comparison* Siponimod vs Placebo

	Siponimod (N'=997)	Placebo (N'=496)	Rate reduction	Rate ratio	95% CI	p-value
Number of new or enlarging T2 lesions (in this scan)**						
Month 12 (relative to baseline)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 24 (relative to Month 12)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of new or enlarging T2 lesions (all post-baseline scans)						
All post-baseline scans	0.70 (0.58; 0.84)	3.60 (3.03; 4.29)	80.6%	0.19	0.16; 0.24	<0.0001

N'=number of patients included in the analysis (i.e. with at least one MRI scan post first dose and non-missing values for the covariates included in the model).
Adjusted mean (rate) refers to the adjusted number of lesions per patient per year. The rate ratio is the ratio of adjusted means (or rate) of siponimod versus Placebo. Rate reduction is derived as (1 - rate ratio) *100.
*Obtained from fitting a repeated measures negative binomial regression model with visit as a categorical factor. Model was adjusted for treatment, region/country, age, baseline number of Gd-enhancing T1 weighted lesions (offset=time between visits).
All post-baseline visits up to and including Month 24 have been included.
Abbreviations: CI: confidence interval; MRI: magnetic resonance imaging.
Source: Kappos et al. 2018;[3] Novartis Data on File (Clinical Study Report for Siponimod).[63]

Percentage brain volume change (PBVC)

The analysis of PBVC relative to baseline is provided by timepoint in Table 18. The PBVC relative to baseline was −0.283% for siponimod and −0.458% for placebo at Month 12 (p<0.0001, unadjusted for multiplicity). The decrease in PBVC was also lower in patients treated with siponimod at Month 24 (p=0.0196, unadjusted for multiplicity).

Table 18: PBVC relative to baseline, by timepoint – repeated measures model

Time-point	Adjusted mean (SE)		Comparison of adjusted means Siponimod vs Placebo			
	Siponimod (N'=894)	Placebo (N'=436)	Rate reduction	Rate ratio	95% CI	p-value
Month 12	−0.283 (0.0264)	−0.458 (0.0341)	0.175	[redacted]	0.103; 0.247	<0.0001
Month 24	−0.711 (0.0356)	−0.839 (0.0476)	0.128	[redacted]	0.021; 0.236	0.0196
Average over Months 12 and 24	−0.50 (95% CI: −0.55; −0.44)	−0.65 (95% CI: −0.72; −0.58)	0.15	-	0.07; 0.23	0.0002

N'=number of subjects included in the analysis (i.e. with at least MRI scan post-baseline and non-missing covariates).
Obtained from fitting a repeated measures model (for normally distributed data) with visit as a categorical factor. Model was adjusted for treatment, country/region, age, normalised brain volume at baseline, number of T1 Gd-enhancing lesions at baseline, T2 volume at baseline, and SPMS group (with/without superimposed relapses, baseline definition).
Adjusted mean refers to PBVC relative to baseline.
All post-baseline visits up to and including Month 36 have been included.
Abbreviations: CI: confidence interval; PBVC: percentage brain volume change; SE: standard error; SPMS: secondary progressive multiple sclerosis.
Source: Kappos et al. 2018;[3] Novartis Data on File (Clinical Study Report for Siponimod).[63]

Further data on T1 hypointense lesions can be found in Appendix L.

B.2.6.4 Relapse-related measures

Siponimod displayed improvement in patients compared with placebo across all relapse-related measures: 55.5% rate reduction for confirmed relapses; delayed time to first relapse; and fewer patients experienced relapses. This represents a meaningful decrease in disease activity in these patients.

Annualised Relapse Rate (ARR)

The adjusted group-based (aggregate) ARRs showed low incidence of relapses in the study population (Table 19). Analysis of adjusted ARR using negative binomial model for confirmed relapses showed a 55.5% rate reduction for confirmed relapses for siponimod compared with placebo (ARR ratio 0.445, p<0.0001).

Table 19: ARR for confirmed relapses – negative binomial regression

Treatment	Adjusted ARR (95% CI)*	Comparison: Siponimod vs Placebo*		
		Rate reduction	ARR ratio (95% CI)	p-value
Siponimod (N=1,099)	0.071 (0.055; 0.092)	55.5%	0.445 (0.337; 0.587)	<0.0001
Placebo (N=546)	0.160 (0.123; 0.207)			

Analysis period: from first day of study drug up to end of core part.
*Obtained from fitting a negative binomial regression model adjusted for treatment, country/region, baseline EDSS, baseline number of T1 Gd-enhancing lesions, and SPMS group (with/without superimposed relapses, baseline definition) (offset: time in analysis period in years).
Abbreviations: ARR: annualised relapse rate; CI: confidence interval; EDSS: Expanded Disability Status Scale.
Source: Kappos et al. 2018.[3]

Time to first relapse

The analysis of time to first confirmed relapse showed a risk reduction of 46.4% that favoured siponimod (HR 0.54, p<0.0001, unadjusted for multiplicity) (Table 20). Time to first confirmed relapse was delayed by siponimod (log rank test, p<0.0001, unadjusted for multiplicity).

Kaplan-Meier curves depicting the percentage of patients who were free of confirmed relapse are provided in Figure 9 (data in Appendix L). The Kaplan-Meier curves show a difference between siponimod and placebo in the percentage of patients free of confirmed relapse and the log rank test indicated a difference between groups (p<0.0001, unadjusted for multiplicity).

Table 20: Time to first confirmed relapse – Cox proportional hazards model

Treatment	n/N'	%	Comparison: Siponimod vs Placebo*		
			Risk reduction	HR (95% CI)	p-value
Siponimod (N=1,099)	113/1,061	(10.7)	46.4%	0.54 (0.41; 0.70)	<0.0001
Placebo (N=546)	100/528	(18.9)			

n/N': n= number of patients with events/N'=number of patients included in the analysis (i.e. with non-missing covariates)

*Using a Cox proportional hazards model with treatment, country/region, baseline EDSS, baseline number of T1 Gd-enhancing lesions, and SPMS group (with/without superimposed relapses, baseline definition) as covariates. Risk reduction is derived as (1- HR) * 100.
Abbreviations: CI: confidence interval; EDSS: Expanded Disability Status Scale; HR: hazard ratio; SPMS: secondary progressive multiple sclerosis.
Source: Kappos et al. 2018;[3] Novartis Data on File (Clinical Study Report for Siponimod).[63]

Figure 9: Percentage of relapse-free (confirmed relapse) subjects – Kaplan-Meier curves

Source: Novartis Data on File (Clinical Study Report for Siponimod).[63]

Proportion of patients with relapse

The proportion of patients with relapse (confirmed relapse and any relapse) is summarised by treatment group in Table 21. Relapses were observed in a lower percentage of patients treated with siponimod ( ) compared with placebo ( ).

Table 21: Proportion of patients with relapse

	Siponimod (N=1,099) n (%)	Placebo (N=546) n (%)
Patients with any relapse (confirmed or unconfirmed)		
Patient with confirmed relapse		

Source: Novartis Data on File (Clinical Study Report for Siponimod).[63]

B.2.6.5 Health-related quality of life

in HRQoL measures were observed for both the physical MSIS-29 scores and EQ-5D utility scores at Month 12. These were to Month 24, however the apparently between-group differences at Month 24 compared with Month 12 should

be interpreted in light of the small sample size and higher variability at Month 24 due to the event-driven trial design.

Multiple Sclerosis Impact Scale (MSIS-29)

A higher score on the MSIS-29 was indicative of greater impact of MS on day-to-day life from a patient's perspective.

For physical impact scores, the adjusted mean differences of [redacted] at Month 12 [redacted] favoured siponimod, but this was [redacted] (Appendix L). The apparently smaller between-group differences at Month 24 compared with Month 12 should be interpreted in light of the small sample size and higher variability at Month 24. The average over all visits for adjusted mean difference was [redacted], which showed a difference (p=[redacted]) favouring siponimod.

For psychological impact scores, statistical [redacted]. The average over all visits for adjusted mean difference was [redacted], which showed a difference (p=[redacted]) favouring siponimod.

EQ-5D-3L

The EQ-5D included a health state classification and a visual analogue scale (VAS) score. The health state classification was converted to a utility index score based on the value set for the UK.

For the EQ-5D utility index scores,[77] the small adjusted mean difference between treatment groups of [redacted] at Month 12 showed a [redacted] favouring siponimod, but this was [redacted] (Appendix L). The changes from baseline in the siponimod group were [redacted] at Month 12 and [redacted] at Month 24 and [redacted] and [redacted] at the respective timepoints in the placebo group. The average over all visits for adjusted mean difference was [redacted], which showed a difference (p=[redacted]) favouring siponimod.

For the VAS score [redacted]

B.2.6.6 Exploratory efficacy results

SDMT has been suggested as the preferred test for assessing cognitive processing speed by the Multiple Sclerosis Outcome Assessments Consortium which developed its recommendations in collaboration with the FDA and EMA.[78] Additionally, among the tests of processing speed, SDMT has the strongest relationship with brain MRI metric that is associated with cognitive performance.[79] As such, SDMT is presented here and additional further exploratory analysis on multiple sclerosis functional composite (MSFC), paced auditory serial addition test (PASAT), brief visuospatial memory test-revised (BVMT-R) and low contrast visual acuity (LCVA) can be found in Appendix L.

Symbol Digit Modalities Test

The score was based on number of correct answers in 90 seconds. At Month 12, the comparison of adjusted mean change in correct responses between siponimod and placebo showed a [redacted], which increased to

[redacted] showing that patients on siponimod had more correct answers in 90 seconds thus showing less deterioration in attention, concentration and processing speed compared with placebo. The difference in adjusted means over all timepoints was [redacted]. There was an improvement in the siponimod group at Month 12 and Month 24, whereas, in the placebo group a worsening of mean scores was observed at each timepoint.

Table 22: Change from baseline in SDMT oral score, by visit – Repeated measures model

	Adjusted means (SE)			Comparison of adjusted means		
Time Point	Siponimod N'=1,019	Placebo N'=516	Difference	SE	95% CI	p-value
Month 6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

N' = number of subjects included in the analysis (i.e. with at least one SDMT score at baseline and post-baseline). Obtained from fitting a repeated measures model for normally distributed data, with visit as categorical factor. Model was adjusted for treatment, country, and baseline SDMT score. Adjusted mean refers to the change from baseline in SDMT score.
All post-baseline visits up to and including Month 30 have been included.
* Indicates statistical significance (2-sided) at the 0.05 level.
Abbreviations: CI: confidence interval; SDMT: symbol digit modalities test; SE: standard error.
Source: Novartis Data on File (Clinical Study Report for Siponimod).[63]

Furthermore, based on a *post hoc* analysis of SDMT oral score data, a lower proportion of participants in the siponimod group than in the placebo group had 6-month confirmed deterioration, measured as a decrease of ≥4 points (with a change of ≥4 points being deemed clinically meaningful). This equates to a 21% risk reduction in 6-month confirmed deterioration in SDMT score of ≥4 points for siponimod compared with placebo (HR 0.79, 95% CI: 0.65–0.96, p=0.0157, unadjusted for multiplicity).[80]

B.2.6.7 Sensitivity analysis of CDP independent of relapse: Estimands analysis

In addition to its efficacy on CDP based on EDSS, siponimod demonstrated a strong effect on inflammatory outcomes such as MRI activity and relapse rate (Section B.2.6.1). Incomplete relapse recovery results in measurable disability progression, potentially skewing the results of CDP, whereas subclinical MRI measures do not directly affect the measurement of CDP. As such, on-study relapses were considered as "intercurrent events" with respect to determining CDP, as discussed in the draft International Conference on Harmonisation (ICH) E9(R1) addendum on estimands and sensitivity analysis in clinical trials.[81] Therefore sensitivity analyses were undertaken on the estimate of effect on CDP unrelated to effect on relapses.

A principal stratum analysis was undertaken to estimate the treatment effect of siponimod on disability progression in non-relapsing patients. This analysis is required as it is not possible to determine the true "non-relapser" subgroup: pre-study non-relapsers may go on to relapse during the study and the on-study non-relapsers group is affected by the treatment effects of siponimod.

Additionally, hypothetical strategies analyses were undertaken to test the separation of the treatment effect on disability progression from that on relapses by assuming either that no relapses happened or that relapses happened equally between arms.

Results of the sensitivity analyses are presented below.

Evaluation of efficacy on CDP in non-relapsing patients

The estimand to address the treatment effect of siponimod on disability progression in non-relapsing patients was defined as follows:

- *Population*: non-relapsers i.e. patients who would not relapse over the specific period of time regardless of treatment assignment (siponimod or placebo), within the targeted SPMS population defined by inclusion/exclusion criteria of EXPAND
- *Variable*: occurrence of 3-month CDP over the specified period of time
- *Intercurrent event*: the intercurrent event of on-study relapse is captured through the population definition
- *Population-level summary*: risk ratio

The non-relapser population of interest is one of four mutually exclusive subgroups, principal strata which are defined according to the potential occurrence of an MS relapse in a given time window:

- *Non-relapsers*: the principal stratum (PS) of patients that would not relapse regardless of treatment
- *Definite relapsers*: the PS of patients that would relapse regardless of treatment
- *Benefiters*: the PS of patients that would relapse if assigned to placebo, and would not relapse if assigned to siponimod
- *Harmed*: the PS of patients that would not relapse if assigned to placebo, and would relapse if assigned to siponimod

It was assumed that no patients fall into the “harmed” principal stratum. This assumption is plausible as given the anti-inflammatory mechanism of siponimod, it is highly unlikely that a patient who would not have relapsed if untreated would experience a relapse if assigned to the Active treatment arm. Deviation from this monotonicity assumption could happen in the presence of rebound effect: this was explored in sensitivity analysis which showed both partial and full relaxation of the monotonicity assumption have negligible impact on the conclusions of the primary principal stratum analysis (data not presented).

The estimation of the proportion of patients in each of the remaining strata and the treatment effect in the “non-relapsing” stratum was carried out with Bayesian logistic regression for the disability progression rate at 12, 18 and 24 months. The regression model was adjusted for baseline EDSS and indicator of relapses in the 2 years prior to study, and the non-relapsing population risk ratios were subsequently obtained by standardisation (Table 23).

Table 23: Effect of siponimod in subgroup of "non-relapsing patients" – principal stratum analysis

Endpoint	Principal stratum – non-relapsers* Estimates of relative risk (posterior median and 95% CrI)		
	12 months	18 months	24 months
3-month CDP	[redacted]	[redacted]	[redacted]
6-month CDP	[redacted]	[redacted]	[redacted]

*Patients who would not relapse over the specified period of time on study regardless of treatment assignment
Abbreviations: CDP: confirmed disability progression; CrI: credible interval.
Source: Novartis Data on File. BAF312A Statistical Overview.[65]

The estimated percentages of non-relapsers range from [redacted] for the time intervals considered, indicating that [redacted] of patients included in this study belong to the non-relapser principal stratum.

Numerically the relative risk for 3-month CDP is between [redacted], indicating a possible [redacted] risk reduction by siponimod treatment not driven by an effect on relapses. This result is consistent with the effect on the overall population for time to 3-months CDP (HR=0.79).

The relative risk for 6-month CDP is between [redacted] indicating a [redacted] risk reduction not driven by an effect on relapses. Six-month CDP is less likely to be driven by relapses. This may explain a RR close but numerically stronger to the HR reported on the overall population (0.74) for time to 6-month CDP.

Treatment effect on disability progression independent of a treatment effect on relapses in the overall population

The question of treatment effect on disability progression independent of an effect on relapses in the overall population is a hypothetical question in the sense of ICH guideline E9 (R1).[81]

Two versions of a hypothetical estimand were defined, denoted as "hypothetical prescriptive" and "hypothetical natural" estimand, respectively. The two versions have the same attributes for population, variable and population-level summary, but differ in the handling of the intercurrent event (relapse). The versions of the main estimand to address the second scientific question of interest were defined as follows:

- *Population* – SPMS population defined by inclusion/exclusion criteria
- *Variable* – Occurrence of 3 month confirmed disability progression over the specified period of time
- *Intercurrent event* – The intercurrent event of on-study relapse will be handled using two hypothetical strategies: assuming no patients would experience intercurrent relapses (hypothetical prescriptive), or assuming patients in both treatment arms would have the same risk of experiencing intercurrent relapses (hypothetical natural)
- *Population-level summary* – HR

An analysis targeting the "hypothetical prescriptive" estimand was provided by a Cox model with censoring at the time of first relapse. The validity of this estimate relied on two assumptions:

- The reasonable assumption that the effect of siponimod on CDP before the first relapse reflects the general effect of siponimod on the course of the disease excluding periods affected by relapsing events (i.e. independent of effect on relapses).
- The assumption that the rate of progressive disability accumulation between relapses is independent from relapse rate. Should this assumption not be valid, the censoring at time of relapse which is strongly related to treatment received would be informative, leading to biased estimates for the standard Cox model. To correct and assess the extent of such potential bias a Cox model with Inverse Probability Censoring Weight (IPCW) was used.

An analysis targeting the "hypothetical natural" estimand was based on a simulation approach where studies are simulated from empirical distributions but with the constraint of having similar relapse rate in both arms.

Of note, the hypothetical prescriptive scenario is meaningful from a clinical perspective as it studies treatment effect on the progressive accumulation of disability between relapsing episodes. On the contrary, the hypothetical natural scenario is difficult to interpret as it focuses on pre- and post-relapse CDP in a situation that ignores one major effect of treatment effect and that will therefore never be observed. For this reason and considering also the strength of the assumptions required for the estimate to be valid, this second analysis should be considered with more caution.

Table 24: Estimation of effect of siponimod on CDP in all patients with SPMS independent of treatment effect on relapses

Endpoint	Cox model with censoring at time of first relapse	Cox model with IPCW*	Simulations based on empirical distribution**
3-month CDP	[redacted]	[redacted]	[redacted]
6-month CDP	[redacted]	[redacted]	[redacted]

*Inverse Probability Censoring Weight; HR estimation and confidence interval.
**HR estimation and confidence interval. Simulation by relapse prognostic levels.
Cox models included baseline EDSS score and presence relapse in the 2 years prior to inclusion as covariates
Abbreviations: CDP: confirmed disability progression; EDSS: Expanded Disability Status Scale; HR: hazard ratio; IPCW: inverse probability censoring weight.

Table 24 shows that the estimated effect for 3-month CDP is [redacted] and becomes [redacted] when correcting bias due to treatment effect on relapses with IPCW. [redacted] is observed on 6-month CDP while for 3-month CDP upper limit of 95% CI is around [redacted].

Simulation results for the hypothetical natural situation show similar or stronger trends in the same direction.

The stability of the HR for 6-month CDP after bias correction confirms the expected lower sensitivity of this endpoint to occurrence of relapses.

B.2.6.8 Open-label extension phase data

Following the core part of the EXPAND trial, all patients were switched on to open-label siponimod, and information on long-term efficacy and safety are being recorded for up to 10 years (the extension part of the trial is still ongoing at the time of this submission).

A RPSFT model was used on the time to CDP Kaplan-Meier curves to correct the placebo arm for crossing over to siponimod treatment, by modelling how the placebo arm would have looked if the placebo patients had not crossed over to open-label siponimod.

Figure 10 presents the Kaplan-Meier curves for time to 6-month CDP for siponimod, the combined core and extension results for the placebo arm, and the RPSFT-corrected placebo-arm data. The HR for 6-month CDP for siponimod compared with RPSFT-corrected placebo after 5.5 years is measured as [redacted] (95% CI: [redacted]).[66] This is compared with a HR of 0.74 (95% CI: 0.60–0.92) at the end of the core part of the EXPAND trial, showing evidence that treatment effect has been observed to be maintained for siponimod over the duration of the extension phase of the trial.

Figure 10: Time to 6-month CDP data from the extension phase of the EXPAND trial

B.2.7 *Subgroup analysis*

Summary of subgroup analysis

- Reduction in the risk of disability progression with siponimod was consistently observed across all pre-planned subgroups
- Due to uncertainty at the point of submission as to the final licenced population for siponimod, a specific subgroup population of Active SPMS is additionally presented; in *post hoc* Active SPMS subgroup analyses:
  - Siponimod treatment delayed the time to both 3- and 6-month CDP in the Active SPMS subgroup compared with placebo (risk reduction of [redacted]% [p=[redacted]] for 3-month CDP, and [redacted]% [p=[redacted]] for 6-month CDP). These outcomes were more favourable for the Active SPMS subgroup than for the intention-to-treat (ITT) population.
  - Siponimod also improved ARR in the Active SPMS subgroup compared with placebo with a [redacted]% risk reduction, p=[redacted]

B.2.7.1 Planned subgroup analyses

Time to 3-month CDP

One of the secondary objectives of the study was to evaluate 3-month CDP (the study primary endpoint) in certain subgroups, specifically:

- Patients with SPMS with or without superimposed relapses
    - Most patients overall had not had relapses within 2 years (63.9%, Table 6) prior to study start
    - The analysis of 3-month CDP was done based on relapses prior to the study and based on relapses during the study
- Patients with or without rapidly evolving disease
    - The “not rapidly evolving” disease subgroup included: patients that were adjudicated for disability progression and patients defined as “not rapidly evolving” based on historical EDSS scores (75.1%) or those with <1.5-point EDSS change in the 2 years prior to study entry
- Patients with multiple sclerosis severity scale (MSSS) score ≥4 (moderate or severe disease course) and MSSS <4 at baseline
    - A majority of patients (82.9%) had a moderate or severe course of disease. Median MSSS was 6

The study was not designed to test for a statistically significant difference between siponimod and placebo in these subgroups. The study was also not designed to test for the consistency of the treatment effect across subgroups.

Additional analyses of time to 3-month CDP were based on the following baseline characteristics:

- Previous interferon β-1b treatment
- Previous MS DMT treatment
- Number of baseline T1 Gd-enhancing lesions
- Baseline EDSS score
- Duration of MS since first symptoms
- Demographic characteristics (gender and age)

A forest plot of time to 3-month CDP depicting the results in the various subgroups can be found in Appendix E. Reduction in the risk of disability progression with siponimod in these subgroups was directionally consistent in all subgroups evaluated with the treatment effect observed in the overall population.

The treatment effect in patients previously treated or not previously treated with any interferon β was directionally consistent with the treatment effect observed in the overall population.

Time to 3-month confirmed worsening in T25FW of at least 20%

The subgroup that showed the most pronounced effect in favour of siponimod was patients with superimposed relapses in the 2 years prior to study start.

Change from baseline in T2 lesion volume

Point estimates in pre-defined subgroups were consistent with the treatment effect in the overall population favouring siponimod over placebo.

Time to 6-month CDP

Reduction in the risk of disability progression observed in the subgroups were directionally consistent with the treatment effect in the overall population, with a similar pattern to the subgroup analysis of time to 3-month CDP (with the exception of patients previously treated with interferon β-1b where the HR was [redacted]; this inconsistent result was based on a relatively small subgroup).

ARR

Relapses were observed during the study in both subgroups: patients with- and without superimposed relapses based on pre-study activity. Fewer relapses were observed in the patients who did not have any relapses in the 2 years prior to study start. Patients with superimposed relapses in the 2 years before baseline who were treated with siponimod had a [redacted] rate reduction in confirmed relapses relative to placebo (ARR ratio=[redacted]) and patients without superimposed relapses in the 2 years before baseline who were treated with siponimod had a [redacted] rate reduction in confirmed relapses relative to placebo (ARR ratio=[redacted]).

B.2.7.2 Active SPMS

Due to uncertainty at the point of submission as to the final licenced population for siponimod, a specific subgroup population of Active SPMS is additionally presented using a *post hoc* analysis. Active SPMS is defined by ongoing relapses and/or MRI activity in patients with SPMS.[9] In the EXPAND trial, the *post hoc* Active SPMS subgroup analyses included patients who experienced relapses in the two years prior to the study and/or who had gadolinium-enhanced T1 lesions at baseline. This choice of subgroup data cut reflected the available baseline characteristics from the EXPAND trial.

Baseline characteristics

A total of [redacted] patients (out of the total trial population of 1,651 patients) made up the Active SPMS subgroup: [redacted] were in the siponimod group and [redacted] in the placebo arm, reflecting the 2:1 randomisation of the overall trial.

The baseline characteristics of patients included in the Active SPMS subgroup of the EXPAND study are presented in Table 25. The full table of baseline characteristics can be found in Appendix E. Patient characteristics at baseline in the subgroup were well balanced between the treatment groups.

Active SPMS is defined by relapses or MRI activity in patients and, as expected, compared with the ITT population, the Active SPMS subgroup of the EXPAND trial included a [redacted] number of

patients experiencing relapses in the previous 2 years prior to screening ([redacted] had no relapses in that time, and [redacted] did not have relapses within the year prior to screening, compared with 63.9% and 78.4%, respectively), a [redacted] percentage of patients with Gd-enhancing T1 lesions ([redacted] compared with [redacted]) and a [redacted] volume of T2 lesions ([redacted] compared with [redacted]). In addition to characteristics related to the definition of Active SPMS, patients in the Active SPMS subgroup had a [redacted] mean age of [redacted] years, compared with 48.0 in the ITT population, but all other baseline characteristics were similar between the subgroup and the overall trial population.

Table 25: Summary of EXPAND baseline characteristics for Active SPMS subgroup

Demographic Variable	Siponimod N=516	Placebo N=263
Age groups – n (%)		
18–40	[redacted]	[redacted]
>40	[redacted]	[redacted]
Age (years)		
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min – Max	[redacted]	[redacted]
Sex – n (%)		
Female	[redacted]	[redacted]
Male	[redacted]	[redacted]
Duration of MS since diagnosis (years)		
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min – Max	[redacted]	[redacted]
Duration of MS since first symptom (years)		
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min – Max	[redacted]	[redacted]
Time since conversion to SPMS (years)		
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min – Max	[redacted]	[redacted]
Number of relapses in the last 2 years prior to screening		
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min – Max	[redacted]	[redacted]
Number of relapses in the last 2 years prior to screening (categories) – n (%)		
None	[redacted]	[redacted]
Number of relapses in the last year prior to screening		
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min – Max	[redacted]	[redacted]

Demographic Variable	Siponimod N=516	Placebo N=263
Number of relapses in the last year prior to screening (categories) – n (%)		
None	[redacted]	[redacted]
Time since the onset of the most recent relapse (months)		
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min – Max	[redacted]	[redacted]
EDSS		
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min – Max	[redacted]	[redacted]
EDSS (categories) – n (%)		
<3.0	[redacted]	[redacted]
3.0–4.5	[redacted]	[redacted]
5.0–5.5	[redacted]	[redacted]
6.0–6.5	[redacted]	[redacted]
>6.5	[redacted]	[redacted]
Number of Gd-enhancing T1 lesions (categories) – n (%)		
0	[redacted]	[redacted]
≥1	[redacted]	[redacted]
Baseline volume of T2 lesions (mm^3)		
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min – Max	[redacted]	[redacted]
Normalised brain volume (cc)		
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min – Max	[redacted]	[redacted]
MS DMTs		
Any MS DMT	[redacted]	[redacted]

Abbreviations: DMT: disease-modifying therapy; EDSS: Expanded Disability Status Scale; MS: multiple sclerosis; SD: standard deviation; SPMS: secondary progressive multiple sclerosis.

Time to 3-month CDP

Siponimod treatment [redacted] the time to 3-month CDP in the Active SPMS subgroup compared with placebo (Table 26, HR [redacted], [redacted]). Kaplan-Meier curves (Figure 11, Appendix L) represent the same results.

Table 26: Active SPMS subgroup: Time to 3-month CDP based on EDSS – Cox proportional hazards model

Treatment	n/N'	(%)	Comparison: Siponimod vs Placebo		
			HR (95% CI)	% Difference	p-value
Siponimod [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo [redacted]	[redacted]	[redacted]			

N=number of subjects in treatment arm and subgroup, n=number of patients with event, N'=number of patients included in the analysis, (i.e. with non-missing covariates).
The Cox regression model includes the predictors treatment and baseline EDSS.
Abbreviations: CDP: confirmed disability progression; CI: confidence interval; EDSS: Expanded Disability Status Scale; HR: hazard ratio; SPMS: secondary progressive multiple sclerosis.

Figure 11: Active SPMS subgroup: Percentage free of 3-month CDP based on EDSS – Kaplan-Meier curves

Last known date to be at risk is defined as the last EDSS assessment date in core part.
Abbreviations: CDP: confirmed disability progression; EDSS: Expanded Disability Status Scale; SPMS: secondary progressive multiple sclerosis.

Time to 6-month CDP

Siponimod treatment [redacted] the time to 6-month CDP in the Active SPMS subgroup compared with placebo (Table 27, HR [redacted], [redacted]). Kaplan-Meier curves (Figure 12, Appendix L) represent the same results.

Table 27: Active SPMS subgroup: Time to 6-month CDP based on EDSS – Cox proportional hazards model

Treatment	n/N'	(%)	Comparison: Siponimod vs Placebo		
			HR (95% CI)	% Difference	p-value
Siponimod [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo [redacted]	[redacted]	[redacted]			

N=number of subjects in treatment arm and subgroup, n=number of patients with event, N'=number of patients included in the analysis, (i.e. with non-missing covariates).
The Cox regression model includes the predictors treatment and baseline EDSS.
Abbreviations: CDP: confirmed disability progression; CI: confidence interval; EDSS: Expanded Disability Status Scale; HR: hazard ratio; SPMS: secondary progressive multiple sclerosis.

Figure 12: Active SPMS subgroup: Percentage free of 6-month CDP based on EDSS – Kaplan-Meier curves

Last known date to be at risk is defined as the last EDSS assessment date in core part.
Abbreviations: CDP: confirmed disability progression; EDSS: Expanded Disability Status Scale; SPMS: secondary progressive multiple sclerosis

ARR

Negative binomial regression analysis of ARR for patients in the Active SPMS subgroup demonstrated an ARR ratio of [redacted] ([redacted]) for siponimod compared with placebo (Table 28).

Table 28: Active SPMS subgroup: Negative binomial regression of ARR for confirmed relapses

Treatment	n/N'	Time (days)	Raw ARR	Adjusted ARR (95% CI)	Comparison: Siponimod vs Placebo		
					ARR Ratio (95% CI)	% Difference	p-value
Siponimod [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo [redacted]	[redacted]	[redacted]	[redacted]	[redacted]			

N=number of subjects in treatment arm and subgroup, n=overall number of relapses in the analysis period for all subjects, N'=number of patients included in the analysis, time = total number of days in the analysis period for all subjects.
The negative binomial includes the predictors treatment and baseline EDSS.
Abbreviations: ARR: annualised relapse rate; CI: confidence interval; EDSS: Expanded Disability Status Scale; SPMS: secondary progressive multiple sclerosis.

Time to first confirmed relapse

Additional data relating to the measure of time to first confirmed relapse can be found in Appendix L.

B.2.8 *Meta-analysis*

Due to the identification of only one study evaluating the efficacy and safety of siponimod in patients with SPMS, no meta-analysis was performed.

B.2.9 *Indirect and mixed treatment comparisons*

Summary of indirect treatment comparison

- An SLR was undertaken to identify trials of DMTs in patients with SPMS. Six RCTs, including EXPAND, met the inclusion criteria of studying a relevant comparator (which is licensed for MS and used in clinical practice for treatment of SPMS) and reporting relevant outcomes. Identified comparator trials included interferon β-1a (Rebif® and Avonex®), interferon β-1b (Betaferon®) and natalizumab.
- Due to differences in trial designs and patient populations, heterogeneity across identified trials in SPMS suggested that a standard network meta-analysis (NMA) approach may be infeasible. To test this in line with NICE Technical Support Document 18, treatment effect modifiers were identified through a combination of clinical opinion and data-driven analyses of the EXPAND individual patient data (IPD). Heterogeneity between EXPAND and comparator trials was identified by pairwise comparisons and standardised mean difference (SMD) tests of the trial characteristics.
- Due to differences in patient populations (inclusion/exclusion criteria and baseline characteristics of treatment effect modifiers) and trial outcomes (dissimilar placebo-arm outcomes), the assumptions of similarity and homogeneity required for an NMA approach were not met.
- The availability of patient-level data for the EXPAND trial allowed individual comparisons to each of the SPMS trials identified, using a MAIC approach; based on recommendations from the NICE Technical Support Document 18, this was deemed likely to lead to less biased comparisons and results than an NMA. However, this was only deemed feasible for the ITT

population and not for the Active SPMS population, where comparator trial baseline characteristics were not reported.

- For each comparator trial, the EXPAND IPD were matched to the comparator trial participants, by excluding EXPAND patients who would not have qualified for the comparator trial. The matched population were then propensity-weighted to adjust for the reported baseline characteristics of the other trial.
- The matching step depends on the inclusion/exclusion criteria reported by comparator trials, which varied by each pairwise comparison, and adjustment was based on the baseline characteristics determined to be treatment effect modifiers.
- Siponimod displayed numerically favourable comparisons to [redacted] for progression measures of 3- and 6-month CDP events (6-month CDP data were not available for all comparator trials); HRs between siponimod and the comparator range from [redacted] for 3-month CDP and [redacted] for 6-month CDP.
- Siponimod also displayed numerically favourable comparison to [redacted], when considering ARR; ARR ratios between siponimod and the comparator range from [redacted] ([redacted]).

B.2.9.1 Identification of comparator trials

An SLR was performed to identify studies of DMTs in patients with SPMS. The details of this SLR are presented in Appendix D.

Study selection

Including EXPAND, six unique RCTs met the inclusion criteria (Table 29) for consideration for ITC by including a relevant comparator (which is licensed for MS and used in UK clinical practice for treatment of SPMS) and reporting relevant outcomes. Justification for excluded trials are reported in Appendix D. For all six RCTs, summary-level data were available (i.e. publications, data from ClinicalTrials.gov, and/or online appendices).

Table 29: List of included trials

Study ID	Author (Year)	NCT Number [b]	Intervention	Citation
EXPAND	Kappos (2018)[3]	NCT01665144	Siponimod	Kappos L, Bar-Or A, Cree BAC, Fox RJ, Giovannoni G et al. (2018) Siponimod vs. placebo in secondary progressive multiple sclerosis (EXPAND): a double-blind, randomised, phase III study. *Lancet* 391 (10127): 1263-1273.
ASCEND	Kapoor (2018)[62]	NCT01416181	Natalizumab	Kapoor R, Ho PR, Campbell N, Chang I, Deykin A et al. (2018) Effect of natalizumab on disease progression in secondary progressive multiple sclerosis (ASCEND): a Phase III, randomised, double-blind, placebo-controlled trial with an open-label extension. *Lancet Neurol* 17 (5): 405-415.

SPECTRIMS	SPECTRIMS Study Group (2001)[82 a]	-	Interferon β-1a (Rebif®)	SPECTRIMS Study Group (2001) Randomized controlled trial of interferon- beta-1a in secondary progressive MS: Clinical results. *Neurology* 56 (11): 1496-1504.
	Li (2001)[83]			Li DK, Zhao GJ, Paty DW (2001) Randomized controlled trial of interferon-beta-1a in secondary progressive MS: MRI results. *Neurology* 56 (11): 1505-1513.
North American Study	Panitch (2004)[54]	-	Interferon β-1b (Betaferon®)	Panitch H, Miller A, Paty D, Weinshenker B (2004) Interferon beta-1b in secondary progressive MS: results from a 3-year controlled study. *Neurology* 63 (10): 1788-1795.
European Study	European Study Group (1998)[84]	-	Interferon β-1b (Betaferon®)	European Study Group (1998) 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* 352 (9139): 1491-1497.
	Kappos (2001)[85 a]			Kappos L, Polman C, Pozzilli C, Thompson A, Beckmann K et al. (2001) Final analysis of the European multicentre trial on IFNbeta-1b in secondary-progressive MS. *Neurology* 57 (11): 1969-1975.
IMPACT	Cohen (2002)[86]	-	Interferon β-1a (Avonex®)	Cohen JA, Cutter GR, Fischer JS, Goodman AD, Heidenreich FR et al. (2002) Benefit of interferon beta-1a on MSFC progression in secondary progressive MS. *Neurology* 59 (5): 679-687.

[a] Indicates the pivotal publication for RCTs for which there are also supporting publications.
[b] Note that ClinicalTrials.gov became available in 2008, and so trials published before this date will not have NCT numbers available.

B.2.9.2 Feasibility assessment: ITT populations

A feasibility assessment was undertaken to determine whether indirect treatment comparisons (ITCs) could be conducted in the absence of direct head-to-head trials comparing siponimod with other DMTs for the treatment of adult patients with SPMS, and to identify suitably comparable studies relative to EXPAND.

The feasibility of conducting ITCs is dependent on the outcomes of interest, the availability of summary-level data and/or individual patient data, similarity of trial designs, and heterogeneity between the studies. Part of the objective was to summarise a qualitative assessment of similarity and heterogeneity based on the study design, inclusion/exclusion criteria, patient characteristics, and study-specific outcome definitions of EXPAND compared with comparator

trials. Following the guidance of the NICE Decision Support Unit (DSU) Technical Support Document (TSD) 18, the feasibility assessment focussed on determining if effect modifiers are present and if there is an imbalance between the trial populations.[87]

Treatment effect modifiers

Treatment effect modifiers were identified through a combination of clinical opinion and data-driven analyses of the EXPAND IPD to assess relationships between covariates and outcomes. Clinical experts experienced in the treatment of MS and in attendance at two Novartis-organised advisory boards (one in the UK, one in Canada) ranked the treatment effect modifiers separately for each outcome in question. The final ranked lists were created from the average of all participating physicians and are presented in Table 30 and Table 31.

Table 30: Treatment effect modifiers identified for CDP

Rank	Adjustment Factor (Treatment Effect Modifier)
1	Age
2	EDSS score at screening
3	Duration of MS since diagnosis
4	Treatment experience (IFN or DMT history)
5	Normalised brain volume
6	Gadolinium-enhancing lesions on T1-weighted images
7	Duration of SPMS
8	Total volume of T2 lesions on T2-weighted images
9	Number of relapses in prior 2 years (or any other relapse variable)
10	Sex

Abbreviations: CDP: confirmed disability progression; DMT: disease-modifying therapy; EDSS: expanded disability status scale; IFN: interferon; MS: multiple sclerosis; SPMS: secondary progressive multiple sclerosis.

Table 31: Treatment effect modifiers identified for ARR

Rank	Adjustment Factor (Treatment Effect Modifier)
1	Time since onset of most recent relapse
2	Number of relapses per patient in one year prior to study
3	Number of relapses per patient in two years prior to study
4	Gadolinium-enhancing lesions on T1-weighted images
5	Total volume of lesions on T2-weighted images

Abbreviations: ARR: annualised relapse rate.

The identified treatment effect modifiers for CDP were additionally tested by univariate regression analysis of the baseline characteristics in EXPAND (the results are presented in Appendix D). The results of these tests, along with univariate exploration of early MAIC results, confirmed that the clinician-ranked lists capture the identifiable effect modifiers within the EXPAND trial data.

Qualitative assessment of imbalance in trial design and baseline patient characteristics

Pairwise comparisons were made to test the following aspects of feasibility: similarity of each comparator trial's study design compared with EXPAND; inclusion and exclusion criteria; outcome definitions; baseline patient characteristics; and consistency of placebo-arm outcomes.

A summary of each of these is presented in Table 32, Table 33, Table 34, Table 35 and Table 36, respectively. Further information on each comparison is provided in Appendix D. Differences were also additionally tested through SMD analyses to quantify the degree of heterogeneity between the trials; results of the SMD analyses are presented in the following section.

For quantitative values, a threshold of +/-10% was chosen to determine whether a characteristic was similar (<10% difference in either direction) or dissimilar (>10% difference in either direction) to EXPAND. This was a subjective judgement and a difference of greater than 10% does not necessarily indicate that the characteristic in question is a driver for bias. A characteristic greater than the 10% threshold was flagged as dissimilar and considered as a potential source of heterogeneity and/or bias, which could present a weakness of indirect comparisons. For quantitative analyses, characteristics were adjusted for irrespective of whether a 10% threshold was observed.

Differences within the threshold of 10% were considered to be similar and marked with a check ("✓"). Differences that exceeded 10% were still considered feasibly comparable (marked with "!") if the criteria in EXPAND was broad enough that the difference could be potentially mitigated by matching or adjusting using IPD. Differences that exceeded 10% and were impossible to accommodate through matching or adjusting were marked with "X" to indicate a potential source of heterogeneity that must be considered in the interpretation of any results, whether summary-level ITC or MAIC.

Table 32: Pairwise comparisons of study design (vs. EXPAND)

Study ID	Study Design	MS Population	Study Duration	Comparator
ASCEND (natalizumab)	✓	✓	!	!
North American Study (IFN β-1b, Betaferon®)	✓	✓	!	!
IMPACT (IFN β-1a, Avonex®)	✓	✓	!	!
SPECTRIMS (IFN β-1a, Rebif®)	✓	✓	✓	!
European Study (IFN β-1b, Betaferon®)	✓	✓	!	!

✓ = Studies are similar; ! = Differences exist between the trials.
Abbreviations: IFN: interferon; MS: multiple sclerosis.

Table 33: Pairwise comparisons of inclusion/exclusion criteria (vs. EXPAND)

Criteria	**ASCEND** (natalizumab)	**North American Study** (IFN β-1b, Betaferon®)	**IMPACT** (IFN β-1a, Avonex®)	**SPECTRIMS** (IFN β-1a, Rebif®)	**European Study** (IFN β-1b, Betaferon®)
MS Population	✓	✓	✓	✓	✓
Baseline EDSS range	✓	✓	!	✓	✓
Age range	!	X	✓	!	!
Prior IFN therapy	✓*	!	!	!	!

Number of relapses in X months prior	✓	X	n/a	X	X
Documented progression within X months prior	!	X	!	!	✓
History of RRMS	n/a	✓	n/a	✓	✓
Duration of MS	n/a	!	n/a	n/a	n/a
Duration of SPMS	!	n/a	n/a	n/a	n/a
MS severity score	!	n/a	n/a	n/a	n/a
T25FW test score	!	n/a	n/a	n/a	n/a

✓ = Criterion is identical; ! = Differences exist between trials and the EXPAND patient population is broader (i.e. matching may be possible); X = Differences exist between the trials and the EXPAND patient population is not broader (i.e. matching is not possible); n/a = not applicable as not reported in the comparator trial.
*ASCEND allowed history of IFN but not within the prior four weeks; EXPAND allowed IFN with no restriction; the four-week restriction could not be matched but this criterion was otherwise considered identical.
Abbreviations: EDSS: expanded disability status scale; IFN: interferon; MS: multiple sclerosis; RRMS: relapsing-remitting multiple sclerosis; SPMS: secondary progressive multiple sclerosis; T25FW: timed 25-foot walk.

Table 34: Pairwise comparisons of outcome definitions (vs. EXPAND)

	ARR	Time to 3-month CDP	Time to 6-month CDP	Discontinuation
ASCEND (natalizumab)	✓	n/a	! *	✓
North American Study (IFN β-1b, Betaferon®)	✓	n/a	!	✓
IMPACT (IFN β-1a, Avonex®)	✓	!	n/a	✓
SPECTRIMS (IFN β-1a, Rebif®)	✓	✓	n/a	✓
European Study (IFN β-1b, Betaferon®)	✓	!	n/a	✓

✓ = Outcome is reported in the comparator trial with the same or very similar definition to EXPAND; ! = Outcome is reported in the comparator trial, but the definition differs from EXPAND; n/a = not applicable as not reported in the comparator trial.
*Because ASCEND reported time to 6-month CDP only as a composite of multiple scales, which is not comparable with the EDSS-specific outcome in other trials such as EXPAND, indirect comparisons for this outcome are instead based on the proportion of patients who experienced 6-month CDP (96 weeks) as measured by the EDSS scale alone.
Abbreviations: ARR: annualised relapse rate; CDP: confirmed disability progression; EDSS: expanded disability status scale; IFN: interferon.

Table 35: Pairwise comparisons of baseline patient characteristics (vs. EXPAND)

Characteristic	**ASCEND** (natalizumab)	**North American Study** (IFN β-1b, Betaferon®)	**IMPACT** (IFN β-1a, Avonex®)	**SPECTRIMS** (IFN β-1a, Rebif®)	**European Study** (IFN β-1b, Betaferon®)
Age (mean years)	✓	✓	✓	!	!
Proportion female (%)	✓	✓	✓	✓	✓
Mean EDSS score	✓	✓	✓	✓	✓
Proportion of patients with EDSS score ≥6.0 (%)	!	n/a	!	n/a	!
Time since onset of MS symptoms (mean years)	✓	n/a	n/a	n/a	n/a
Duration of MS (mean years)	✓	!	!	✓	✓
Duration of SPMS (mean years)	!	✓	n/a	✓	!
Normalised brain volume (mean cm^3)	✓	n/a	n/a	n/a	n/a
Proportion of patients with Gd+ lesions of T1-weighted images (%)	!	n/a	!	n/a	n/a
Total volume of T2 lesions on T2-weighted images (mean mm^3)	✓	n/a	n/a	n/a	n/a
Proportion of patients without previous use of a DMT (%)	n/a	n/a	n/a	n/a	n/a
Mean T25FW Test (seconds)	!	n/a	!	n/a	n/a
Time since most recent relapse (months)	✓	n/a	!	n/a	n/a
Proportion of patients relapse-free in prior year (%)	✓	n/a	!	n/a	n/a
Proportion of patients relapse-free in prior 2 years (%)	✓	!	n/a	!	!
Number of relapses per patient in the prior year (mean)	n/a	n/a	!	n/a	n/a
Number of relapses per patient in the previous 2 years (mean)	n/a	!	n/a	!	n/a

✓ = Both studies report the characteristic and the values are similar (within 10%); ! = Both studies report the characteristic and the values are dissimilar (by >10%); n/a = not applicable as not reported in the comparator trial.
Abbreviations: DMT: disease modifying therapy; EDSS: expanded disability status scale; Gd+: gadolinium-enhancing; IFN: interferon; MS: multiple sclerosis; RRMS: relapsing-remitting multiple sclerosis; SPMS: secondary progressive multiple sclerosis; T25FW: timed 25-foot walk.

Table 36: Pairwise comparisons of placebo-arm outcomes* (vs. EXPAND)

Study ID	ARR	Annualised Rate of Discontinuation
ASCEND (natalizumab)	✓	!
North American Study (IFN β-1b, Betaferon®)	!	!
IMPACT (IFN β-1a, Avonex®)	!	!
SPECTRIMS	!	!

(IFN β-1a, Rebif®)		
European Study (IFN β-1b, Betaferon®)	!	!

✓ = Outcome value is similar (within 10%) compared to EXPAND; ! = Outcome value is dissimilar (>10% different) compared to EXPAND.
*The placebo-arm results for ARR and discontinuation were compared because these outcomes are reported by trial arm, whereas the time-to-event outcomes (i.e., CDP-3 and CDP-6) are generally reported only as an HR between a treatment arm and the placebo arm.
Abbreviations: ARR: annualised relapse rate; IFN: interferon.

SMD assessment of imbalance in patient characteristics

SMD were also used to quantify the degree of heterogeneity between the trials for each baseline characteristic when compared to EXPAND. These are presented in Table 37 and demonstrate similar results to the qualitative 10% threshold analysis presented above. Both sets of analyses demonstrate there are moderate-to-major differences between EXPAND and the comparator trials.

Table 37: Imbalances in baseline characteristics between EXPAND and comparator trials based on SMD

Baseline patient characteristics	**EXPAND** (siponimod)	**ASCEND** (natalizumab)	**North American Study** (IFN β-1b, Betaferon®)	**IMPACT** (IFN β-1a, Avonex®)	**SPECTRIMS** (IFN β-1a, Rebif®)	**European Study** (IFN β-1b, Betaferon®)
Age (mean years)	48	47.2	46.8	47.6	42.8	41
Proportion female (%)	60	62	63	64	63	61
Mean EDSS score	5.4	5.6	5.1	5.2	5.4	5.1
Proportion of patients with EDSS score ≥6.0 (%)	56	63	n/a	48	n/a	45
Time since onset of MS symptoms (mean years)	16.8	16.5	n/a	n/a	n/a	n/a
Duration of MS (mean years)	12.6	12.1	14.7	16.5	13.3	13.1
Duration of SPMS (mean years)	3.8	4.8	4.0	n/a	4.0	2.2
Normalised brain volume (mean cm^3)	1,423	1,423	n/a	n/a	n/a	n/a
Proportion of patients with Gd+ lesions of T1-weighted images (%)	21	24	n/a	36	n/a	n/a
Total volume of T2 lesions on T2-weighted images (mean mm^3)	15,321	16,793	n/a	n/a	n/a	n/a
Proportion of patients without previous use of a DMT (%)	[redacted]	23	100*	100*	100*	100
Mean Timed 25-Foot Walk Test (seconds)	[redacted]	n/a	n/a	14.5	n/a	n/a
Time since most recent relapse (months)	[redacted]	57	n/a	44.4	n/a	n/a
Proportion of patients relapse-free in prior year (%)	[redacted]	84	n/a	61	n/a	n/a

Proportion of patients relapse-free in prior 2 years (%)	[redacted]	71	55	n/a	53	30
Number of relapses per patient in the prior year (mean)	0.2	n/a	n/a	0.6	n/a	n/a
Number of relapses per patient in the previous 2 years (mean)	0.7	n/a	0.8	n/a	0.9	n/a

Green = minimal degree of difference (SMD <0.1); orange = moderate degree of difference (SMD ≥0.1 and <0.2); red = major degree of difference (SMD ≥0.2). SMD thresholds based on Austin 2009.[88]
Characteristics marked n/a if not reported in the comparator trial.
*A value of 100% was assumed because IFN-experienced patients were excluded at screening, as described in the exclusion criteria of the trial, and other DMTs were not available at the time of enrolment.
Abbreviations: DMT: disease-modifying therapy; EDSS: Expanded Disability Status Scale; Gd+: gadolinium-enhancing; IFN: interferon; MS: multiple sclerosis; n/a: not applicable; SMD: standardised mean difference; SPMS: secondary progressive multiple sclerosis.

Conclusions

A summary of the conclusions of the ITC feasibility assessments are presented in brief below (Table 38). Additional information and full details for the pairwise feasibility assessments can be found in Appendix D.

It is notable that, in addition to the feasibility assessment presented here, the independent US-based Institute for Clinical and Economic Review (ICER) assessment of siponimod in people with SPMS arrived at the same conclusion, namely that summary-level indirect comparisons were infeasible for siponimod and the comparators discussed.[89]

Table 38: Summary of conclusions of the ITC feasibility assessments

Study ID	Key Sources of Potential Bias when Compared with EXPAND	Conclusions / Recommendations
SPECTRIMS North American Study European Study IMPACT	• Excluded IFN-experienced patients • Several major differences in inclusion/exclusion criteria • Several major differences in baseline patient characteristics • Inconsistencies in placebo-arm outcomes	• Summary-level ITCs may have low validity due to significant imbalance in patient populations • However, the populations overlap generously with EXPAND • Outcome definitions are reasonably similar where reported, with some caveats • Therefore, conduct MAICs to account for heterogeneity where possible
ASCEND	• Some differences in inclusion/exclusion criteria • Some differences in baseline patient characteristics • Major difference in definitions of outcomes pertaining to time to CDP	• Summary-level ITCs may have reduced validity due to imbalance in patient populations • However, the populations overlap generously with EXPAND • With the exception of time to CDP (either measure), outcome definitions are reasonably similar where reported • Therefore, conduct MAICs to account for heterogeneity where possible

Abbreviations: CDP: confirmed disability progression; IFN: interferon; ITC: indirect treatment comparison; MAIC: matching-adjusted indirect comparison.

Although creation of a connected network may initially seem possible through the connection of placebo arms between the trials of interest, the heterogeneity observed across identified trials in SPMS lead to a standard NMA approach being infeasible. The presence of significant clinical heterogeneity, inconsistency and dissimilarity, as well as an imbalance of effect modifiers between EXPAND and each of the comparator trials undermines the validity of ITC methods that are based on summary-level data, such as an NMA. Failure to account for differences in trial designs and effect modifiers between trial populations can lead to misleading comparisons of treatment effect and can result in significant bias and clinically implausible results as a result of differences in the prognosis and treatment effect of disparate patient populations. For the five included comparator studies (i.e., SPECTRIMS, the North American Study, the European Study, ASCEND, and IMPACT), following the guidance of the NICE DSU TSD18, anchored MAICs were determined to be the most appropriate and robust comparative method because the majority of important clinical differences between the trials could be adjusted for using MAIC methodology through use of IPD from EXPAND. Despite the caveat that not all differences could be accounted for, MAICs would still provide the most appropriate method for indirect comparisons.

B.2.9.3 Feasibility assessment: Active SPMS sub-group

A feasibility assessment for ITCs for the Active SPMS subgroup was also conducted for each comparator trial. Pairwise comparisons to determine the similarity of the definition of Active SPMS and the baseline patient characteristics can be found in Table 39 and Table 40, respectively.

Baseline characteristics were not reported for the Active SPMS subgroup in the SPECTRIMS trial. Therefore, it would have to be assumed that the characteristics for the overall population could be applied to the Active subgroup when conducting a MAIC. Given that this assumption is unlikely to be true, with patients with Active SPMS by definition having a higher disease activity at baseline, in combination with the characteristics of the overall study population not aligning as closely with the EXPAND Active SPMS population as with the overall EXPAND population, a MAIC focusing on Active SPMS specifically is not possible.

Neither the North American study nor the ASCEND trial reported an Active SPMS subgroup and the overall populations were not considered to represent an Active SPMS population closely enough for a MAIC or ITC in this population to be robust.

For the European study and the IMPACT trial, as neither baseline characteristics nor relevant outcomes were reported for the Active SPMS subgroup, MAICs were not deemed feasible.

Further information on each comparison is provided in Appendix D.

Table 39: Pairwise comparisons of Active SPMS definition (vs. EXPAND Active SPMS subgroup)

	Active SPMS Definition	Comparability
EXPAND	Presence of relapses in 2 years before study or Gd+ T1 lesions at baseline	
SPECTRIMS (IFN β-1a, Rebif®)	Presence of relapses in the 2 years preceding the study	!

North American Study (IFN β-1b, Betaferon®)	None	n/a
European Study (IFN β-1b, Betaferon®)	Relapse within 2 years before the study	!
ASCEND (natalizumab)	None	n/a
IMPACT (IFN β-1a, Avonex®)	Presence of relapses in year before enrolment	!

! = Differences exist between trials and the EXPAND patient population is broader (i.e. matching may be possible)
Abbreviations: Gd+: gadolinium-enhancing; IFN: interferon; SPMS: secondary progressive multiple sclerosis.

Table 40: Pairwise comparisons of baseline patient characteristics (comparator ITT vs. EXPAND Active SPMS subgroup)

Characteristic	**SPECTRIMS** (IFN β-1a, Rebif®)	**North American Study** (IFN β-1b, Betaferon®)	**European Study** (IFN β-1b, Betaferon®)	**ASCEND** (natalizumab)	**IMPACT** (IFN β-1a, Avonex®)
Age (mean years)	✓	✓	!	✓	✓
Proportion female (%)	!	!	!	!	!
Mean EDSS score	✓	✓	✓	✓	✓
Proportion of patients with EDSS score ≥6.0 (%)	n/a	n/a	!	!	!
Time since onset of MS symptoms (mean years)	n/a	n/a	n/a	✓	n/a
Duration of MS (mean years)	!	!	!	✓	!
Duration of SPMS (mean years)	!	!	✓	!	n/a
Normalised brain volume (mean cm3) c	n/a	n/a	n/a	✓	n/a
Proportion of patients with Gd+ lesions of T1-weighted images (%)	n/a	n/a	n/a	!	!
Total volume of T2 lesions on T2-weighted images (mean mm3)	n/a	n/a	n/a	✓	n/a
Proportion of patients without previous use of a DMT (%)	n/a	n/a	n/a	n/a	n/a
Mean T25FW (seconds)	n/a	n/a	n/a	!	!
Time since most recent relapse (months)	n/a	n/a	n/a	!	!
Proportion of patients relapse-free in prior year (%)	n/a	n/a	n/a	!	!
Proportion of patients relapse-free in prior 2 years (%)	!	!	!	!	n/a

Number of relapses per patient in the prior year (mean)	n/a	n/a	n/a	n/a	!
Number of relapses per patient in the previous 2 years (mean)	!	!	n/a	n/a	n/a

✓ = Both studies report the characteristic and the values are similar (within 10%); ! = Both studies report the characteristic and the values are dissimilar (by >10%).
Abbreviations: DMT: disease modifying therapy; EDSS: expanded disability status scale; Gd+: gadolinium-enhancing; IFN: interferon; MS: multiple sclerosis; RRMS: relapsing-remitting multiple sclerosis; SPMS: secondary progressive multiple sclerosis; T25FW: timed 25-foot walk.

B.2.9.4 Matching-adjusted indirect treatment comparisons (MAICs)

MAICs were conducted using the methods outlined in the NICE DSU TSD18.[87] The MAIC method is designed to reduce cross-trial differences in baseline patient characteristics and reduce sensitivity to effect measures. Individual patient data from one trial (i.e. EXPAND) were weighted to match mean baseline characteristics (i.e. aggregate or summary data) as published from the included trials identified in the systematic review. Results of the trial with IPD were then reanalysed using the weighted patient-level data set.

This MAIC method was used to carry out "anchored" indirect comparisons, where there is a common comparator arm in each trial (in all cases in this submission the common comparator was placebo).

Matching was performed to align the population of EXPAND to the reported inclusion and exclusion criteria of trials pertaining to the comparator DMT by excluding EXPAND patients who would not have qualified for the comparator trials, where possible.

The matching step depends on the inclusion/exclusion criteria reported by comparator trials. As such, the precise list of factors matched varies by pairwise comparison. Only criteria reported by the comparator trial were matched (where possible). If the criterion was not described by the comparator trial or was already identical to EXPAND, it was not necessary to match.

Given that the comparisons were anchored, adjustment was only required for treatment effect modifiers; this was conducted using all the available clinically relevant baseline characteristics identified as treatment effect modifiers in Table 30 and Table 31, for CDP and ARR respectively. The identified characteristics were ranked by relative importance, as presented in Table 30 and Table 31, and were used to re-weight the outcomes of patients of the already-matched EXPAND population to simultaneously adjust the mean of all chosen treatment effect modifiers or "adjustment factors" (e.g. mean EDSS score at baseline).

MAIC results are presented herein for all feasible comparisons with siponimod, disaggregated by DMT, dose, and regimen: IFN β-1a (Rebif®) 22 µg three times weekly (TIW), IFN β-1a (Rebif®) 44 µg TIW, IFN β-1b (Betaferon®) 250 µg every other day (Q2D), natalizumab 300 mg every 4 weeks (Q4W), and IFN β-1a (Avonex®) 60 µg once weekly (QW) (unlicensed dose, see below for rationale).

Avonex® 60 µg is not the licensed regimen of this treatment, however the Summary of Product Characteristics (SmPC) for Avonex® states that no additional benefit has been shown by administering a higher dose once a week, and so it can be assumed that the efficacy of the 60 µg dose, for which there is RCT data available in SPMS, is the same as for the licensed 30 µg dose.[90] The inclusion of Avonex® 60 µg data to inform the Avonex comparison was also validated

by a clinical expert approached by Novartis (a Consultant Neurologist with substantial experience in MS research and clinical trials). Additionally, whilst Betaferon® is not recommended by NICE, Extavia® is the same DMT sold under a different brand name and does have positive NICE recommendation (TA527).[52]

The matching and adjustment process (propensity score reweighting) for each pairwise comparison is reported in greater detail in Appendix D. Please refer to Section B.2.9.2 and Appendix D for a detailed breakdown of the imbalance in inclusion criteria and baseline patient characteristics between studies. The full results of each MAIC (including scenario analyses exploring removing the lowest-ranked treatment effect modifiers from the adjustment one-by-one) are presented in Appendix D, with a summary of results presented below.

Summary of Results

Summaries of all the most conservative (i.e. fully matched and adjusted) MAIC results, which were used in the base case of the cost-effectiveness model, are presented in Table 41 for the outcomes of 3- and 6-month CDP, and in Table 42 for the outcome of ARR.

Table 41: Summary of MAIC Results for 3- and 6-month CDP

Comparator Intervention	Regimen	Study ID(s)	Published Effect Estimates (95% CI) [c]			MAIC Results (95% CI) [d]		
			Type	Comparator vs. Placebo [c]	Siponimod vs. Placebo [c]	Type	Siponimod vs. Comparator	Siponimod vs. Placebo
Time to 6-month CDP								
Betaferon® (SC IFNβ-1b)	250 µg Q2D	North American Study	HR	0.92 (0.71–1.20) [a]	**0.74 (0.60 to 0.92)**	HR	[redacted]	[redacted]
Proportion with 6-month CDP (96w) [b]								
Natalizumab	300 mg Q4W	ASCEND	OR	1.06 (0.74–1.53) [b]	[redacted]	OR	[redacted]	[redacted]
Time to 3-month CDP								
Rebif® (SC IFNβ-1a)	22 µg TIW	SPECTRIMS	HR	0.88 (0.69–1.12) [a]	**0.79 (0.65 to 0.95)**	HR	[redacted]	[redacted]
	44 µg TIW	SPECTRIMS	HR	0.83 (0.65–1.07)		HR	[redacted]	
Betaferon® (SC IFNβ-1b)	250 µg Q2D	European Study	HR	0.74 (0.60–0.91) [a]		HR	[redacted]	[redacted]
Avonex® (IM IFNβ-1a)	*60 µg QW**	IMPACT	HR	0.977 (0.68–1.41)		HR	[redacted]	[redacted]

Note: An effect size of <1 indicates that the intervention has a favourable outcome relative to the comparator or placebo. Statistically significant values are bolded.
[a] The HR and/or CI were not reported in the publication. Missing values were estimated using either the reported HR and p-value, the reported Kaplan-Meier curve through curve-fitting, or through analysis of IPD, as appropriate.
[b] The proportion of patients who experienced 6-month CDP by 96 weeks based on an increase in EDSS alone. For EXPAND, the proportion of patients with this outcome was calculated using the IPD, based on a conservative assumption that all patients censored at or before 96 weeks had experienced a 6-month CDP event.
[c] Extracted or derived from the EXPAND or comparator publication(s).
[d] The target population is that of the comparator trial.
* This is an unlicensed dose, however the SmPC for Avonex® states that 'no additional benefit has been shown by administering a higher dose (60 µg) once a week.'
Abbreviations: CDP: confirmed disability progression; CI: confidence interval; HR: hazard ratio; IFNβ: interferon beta; IM: intramuscular; IPD: individual patient data; MAIC: matching-adjusted indirect comparison; OR: odds ratio; Q2D: once every other day; QW: once weekly; Q4W: once every four weeks; SC: subcutaneous; TIW: three times weekly.

Table 42: Summary of MAIC Results for ARR

Comparator Intervention	Regimen	Study ID(s)	Published Effect Estimates (95% CI) [a]			MAIC Results (95% CI) [b]		
			Type	Comparator vs. Placebo [a]	Siponimod vs. Placebo [a]	Type	Siponimod vs. Comparator	Siponimod vs. Placebo
Betaferon® (SC IFNβ-1b)	250 µg Q2D	North American Study European Study [d]	RR	**0.65 (0.48–0.88)**	**0.45 (0.34 to 0.59)**	RR	[redacted]	[redacted]
Rebif® (SC IFNβ-1a)	22 µg TIW	SPECTRIMS	RR	**0.69 (0.56–0.84)**		RR	[redacted]	[redacted]
	44 µg TIW	SPECTRIMS	RR	**0.69 (0.56–0.85)**		RR	[redacted]	
Natalizumab	300 mg Q4W	ASCEND	RR	**0.453 (0.32–0.63)**		RR	[redacted]	[redacted]
Avonex® (IM IFNβ-1a)	60 µg QW*	IMPACT	RR	**0.67 (0.49–0.90)** [c]		RR	[redacted]	[redacted]

Note: An effect size of <1 indicates that the intervention has a favourable outcome relative to the comparator or placebo. Statistically significant values are bolded.
[a] Extracted or derived from the EXPAND or comparator publication(s).
[b] The target population is that of the comparator trial.
[c] Error was calculated from the reported RR and p-value.
[d] Error has been estimated using the CI from the North American Study 160 µg/m^2 treatment arm which has a similar effect size and sample size. The Handling Continuous Outcomes in Quantitative Synthesis (Fu et al., 2013) guide recommends that studies only missing error should not be excluded as this can lead to a biased combined estimate.
[e] Matched only (could not adjust).
* This is an unlicensed dose, however the SmPC for Avonex® states that 'no additional benefit has been shown by administering a higher dose (60 µg) once a week.'
Abbreviations: ARR: annualised relapse rate; CI: confidence interval; HR: hazard ratio; IFNβ: interferon beta; IM: intramuscular; Q2D: once every other day; QW: once weekly; Q4W: once every four weeks; RR: rate ratio; SC: subcutaneous; TIW: three times weekly.

Conclusions of the MAICs

Given the imbalance observed and presence of effect modifiers between EXPAND and the comparator trials, MAICs allow for the best use of all the efficacy data available in SPMS, in a fair and adjusted comparison.

Matching the EXPAND IPD to comparator trials reduced the effective sample size to approximately [redacted] depending on criteria of the trial(s) available for each DMT. This illustrates the magnitude of dissimilarity between the included/excluded patients of each trial relative to EXPAND, which underscores the inadequacy of unadjusted summary-level ITC methods for comparing these heterogeneous trials.

Despite the reduction in sample size, siponimod demonstrated [redacted]. In particular, siponimod was determined to be [redacted] for the outcome of time to 6-month CDP compared with Betaferon®, and this result was [redacted]. Siponimod was [redacted] regarding the proportion of patients with 6-month CDP at 96 weeks compared with natalizumab, and the outcome of time to 3-month CDP compared with Betaferon®, Avonex®, and both regimens of Rebif® (22 or 44 µg TIW).

For the outcome of ARR, siponimod was [redacted] to Avonex®, both regimens of Rebif®, and Betaferon®. Siponimod was [redacted] with regards to ARR in the comparison with natalizumab, [redacted] with regards to CPD noted above.

Generalisability of the MAIC results to Active SPMS subgroup

Although a separate MAIC in the Active SPMS subgroup itself is infeasible (see Section B.2.9.3), the results of the matching and adjusting process show that the base case comparison to Extavia is selective for a more active subset of the EXPAND trial: average age and baseline EDSS are lowered, the proportion of patients experiencing relapses in the two years prior to the trial is increased, as is the average number of relapses per patients in the two years prior to the trial. Therefore, although the extrapolation of the MAIC results to the Active SPMS subgroup has inherent limitations, it remains preferable to an unadjusted naïve comparison of subgroup data between two trials which are known to differ in many respects, as laid out in Section B.2.9.2 and B.2.9.3.

B.2.9.5 Uncertainties in the indirect and mixed treatment comparisons

EXPAND included patients with prior history of interferon therapy while SPECTRIMS, the North American Study, the European Study, and IMPACT did not. The only study in SPMS besides EXPAND that included IFN-experienced patients was ASCEND. The potential bias of including only IFN-naïve patients is unknown; however, approximately [redacted]% of the patients in EXPAND were IFN-experienced; in other words, the majority of the patients in EXPAND have [redacted] treatment history than the populations of these five studies; in part this reflects the large distance in time between the interferon studies and the more recent EXPAND and ASCEND studies. Additionally, IFN-naïve patients may have different demography or disease history than IFN-experienced patients. For instance, the mean duration of MS or duration of SPMS at baseline were significantly shorter in several trials than in EXPAND, including the North American Study (duration of MS only), the European Study (duration of SPMS only), and IMPACT (duration of MS only; duration of SPMS was not reported).

The matched comparison with ASCEND included the largest effective sample size, reflecting that ASCEND included the most similar population to EXPAND. Adjusting the EXPAND IPD for the ranked factors reduced the sample size further by necessity in every pairwise comparison. This issue reflects differences between the patient populations of comparator trials and EXPAND and is an inherent limitation of the MAIC results for all comparisons.

MAICs for the outcome of treatment discontinuation were explored in the feasibility assessment, but treatment effect modifiers related to adverse events and discontinuation were not well reported in comparator studies, thereby precluding a valid MAIC. For example, history of gastrointestinal problems may be associated with discontinuations but is not commonly reported in MS studies and cannot therefore be adequately adjusted for.

Despite some limitations, using anchored MAICs still had an advantage over summary-level ITCs because they consider a combination of IPD and aggregate data to account for observed differences among the design and population of the trials, thereby providing a more robust comparison.

B.2.10 *Adverse reactions*

Summary of safety and tolerability of siponimod

- The safety of siponimod was evaluated through the assessment of TEAEs, defined as starting on or after the day of first dose of study medication, and included up to 30 days after double-blind study drug discontinuation or the day before the start of open-label siponimod, whichever came first.
- TEAEs were observed in the majority of patients and in a higher percentage of patients randomised to siponimod (88.7%) than placebo (81.5%)
- The most frequently reported TEAEs (in at least 10% of patients per group) were: headache, nasopharyngitis, urinary tract infection, and fall. The TEAEs reported more frequently in the siponimod group than in placebo (by ≥2%) include dizziness, nausea, diarrhoea, alanine aminotransferase, gamma-glutamyl transferase increased, hypertension and oedema peripheral.
- Overall, [redacted]% of patients had Grade 3/4 TEAEs ([redacted]% siponimod, [redacted]% placebo).
- TEAEs that led to temporary interruption of study drug occurred in a small percentage of patients: [redacted]% in the siponimod group and [redacted]% in the placebo group.
- A total of [redacted]% of patients in the siponimod group and [redacted]% in the placebo group had TEAEs leading to study drug discontinuation. The most common of these were: macular oedema, alanine aminotransferase increased, and bradycardia.
- A total of nine patient deaths were reported during the study, including one patient who died during screening. All deaths were deemed to be unrelated to study treatment.
- Overall, siponimod was well tolerated, with an acceptable TEAE profile.

B.2.10.1 Safety results informing the decision problem

The safety of siponimod in patients with SPMS was evaluated in the EXPAND trial. 1,645 patients were included in the safety set: 1,099 on siponimod and 546 on placebo. This comprised all patients who received at least one dose of study medication.

Following randomisation, patients underwent 6-day titration to the target maintenance dose of blinded study drug (2 mg siponimod or placebo). A total of 210 patients switched to open-label siponimod as rescue treatment and were titrated at the time of the switch.

Patients randomised to siponimod had similar mean exposure to double-blind study drug ([redacted]) compared with placebo ([redacted]). Acknowledging the 2:1 randomisation ratio, cumulated exposure to siponimod was [redacted] patient-years vs [redacted] patient-years in placebo. Most patients in each group (80.4% siponimod, 78.8% placebo) had at least 12 months of exposure to double-blind study drug; however, less than 30% of patients in either group had at least 24 months of exposure, this was due to the event-driven study design leading to variable exposure duration for different patients.

Mean exposure to open-label siponimod was [redacted] months for the [redacted] patients initially randomised to siponimod and [redacted] months for the [redacted] patients who switched to open-label siponimod from placebo. Patient-years of exposure to open-label siponimod were [redacted] in the siponimod group and [redacted] in the patients who switched from placebo.

The safety of siponimod was evaluated through the assessment of TEAEs, defined as starting on or after the day of first dose of study medication. The common terminology criteria for adverse events (CTCAE, Grades 1–4) were used in this study for investigator assessments of AE severity. When CTCAE grading did not exist for an AE, sites were instructed to use Grade 1 for mild, Grade 2 for moderate, Grade 3 for severe, and Grade 4 for life-threatening.

Summaries of safety data included data up to 30 days after double-blind study drug discontinuation or the day before start of open-label siponimod, whichever came first.

B.2.10.2 Treatment-emergent adverse events

TEAEs were observed in the majority of patients and in a higher percentage of patients randomised to siponimod (88.7%) than placebo (81.5%) (Table 43). Almost half of the patients in each group had TEAEs in the infections and infestations systems organ class (SOC). The 2 SOCs with the greatest magnitude of difference (>5%) between treatment groups were: nervous system disorders ([redacted] siponimod, [redacted] placebo) and investigations ([redacted] siponimod, [redacted] placebo).

Table 43: Patients with TEAEs, by primary SOC

Primary SOC	Siponimod N=1,099, n (%)	Placebo N=546, n (%)
Number of patients with at least one AE	**975 (88.7)**	**445 (81.5)**
Infections and Infestations	539 (49.0)	268 (49.1)
Nervous System Disorders	[redacted]	[redacted]
Musculoskeletal and Connective Tissue Disorders	[redacted]	[redacted]
Gastrointestinal Disorders	[redacted]	[redacted]
General Disorders and Administration Site Conditions	[redacted]	[redacted]
Investigations	[redacted]	[redacted]
Injury, Poisoning and Procedural Complications	[redacted]	[redacted]
Skin and Subcutaneous Tissue Disorders	[redacted]	[redacted]
Psychiatric Disorders	[redacted]	[redacted]

Vascular Disorders	[redacted]	[redacted]
Cardiac Disorders	[redacted]	[redacted]
Respiratory, Thoracic and Mediastinal Disorders	[redacted]	[redacted]
Neoplasms Benign, Malignant and Unspecified (Including Cysts and Polyps)	[redacted]	[redacted]
Eye Disorders	[redacted]	[redacted]
Metabolism and Nutrition Disorders	[redacted]	[redacted]
Renal and Urinary Disorders	[redacted]	[redacted]
Ear and Labyrinth Disorders	[redacted]	[redacted]
Blood and Lymphatic System Disorders	[redacted]	[redacted]
Reproductive System and Breast Disorders	[redacted]	[redacted]
Hepatobiliary Disorders	[redacted]	[redacted]
Endocrine Disorders	[redacted]	[redacted]
Immune System Disorders	[redacted]	[redacted]
Congenital, Familial and Genetic Disorders	[redacted]	[redacted]
Social Circumstances	[redacted]	[redacted]
Product Issues*	[redacted]	[redacted]

A patient with multiple occurrences of an AE or with multiple AEs within a primary SOC is counted only once in this SOC category.
Primary SOC are sorted in descending frequency of AEs in the siponimod column.
*The TEAEs under the 'product issues' category were breast implant breakage and dental prosthesis breakage.
Abbreviations: AE: adverse event; SOC: systems organ class; TEAE: treatment-emergent adverse event.
Source: Kappos et al. 2018;[3] Novartis Data on File (Clinical Study Report for Siponimod).[63]

The TEAEs reported in ≥3% of patients in the siponimod group are presented in Table 44. The most frequently reported TEAEs (in at least 10% of patients per group) were: headache, nasopharyngitis, urinary tract infection, and fall. The TEAEs reported more frequently in the siponimod group than in placebo (by ≥2%) include [redacted].

Table 44: Patients with most frequently reported TEAEs (at least 3% in any treatment group)

Preferred Term	Siponimod N=1,099, n (%)	Placebo N=546, n (%)
Number of patients with at least one AE	**975 (88.7)**	**445 (81.5)**
Headache	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]
Urinary Tract Infection	[redacted]	[redacted]
Fall	[redacted]	[redacted]
Hypertension	115 (10.5)	41 (7.5)
Fatigue	[redacted]	[redacted]
Upper Respiratory Tract Infection	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]
Nausea	[redacted]	[redacted]
Influenza	[redacted]	[redacted]

Diarrhoea	[redacted]	[redacted]
Back Pain	[redacted]	[redacted]
Alanine Aminotransferase Increased	[redacted]	[redacted]
Pain in Extremity	[redacted]	[redacted]
Bradycardia	50 (4.5)	14 (2.6)
Oedema Peripheral	50 (4.5)	13 (2.4)
Arthralgia	[redacted]	[redacted]
Depression	[redacted]	[redacted]
Melanocytic Naevus	[redacted]	[redacted]
Gamma-Glutamyl Transferase Increased	[redacted]	[redacted]
Muscle Spasticity	[redacted]	[redacted]
Constipation	[redacted]	[redacted]
Insomnia	[redacted]	[redacted]
Muscle Spasms	[redacted]	[redacted]
Bronchitis	[redacted]	[redacted]
Contusion	[redacted]	[redacted]
Cough	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]
Vertigo	[redacted]	[redacted]
Gait Disturbance	[redacted]	[redacted]
Oropharyngeal Pain	[redacted]	[redacted]
Paraesthesia	[redacted]	[redacted]

A patient with multiple occurrences of an AE or with multiple AEs within a preferred term is counted only once in this preferred term category.
Preferred terms are sorted in descending frequency of AEs in the siponimod column.
Abbreviations: AE: adverse event; TEAE: treatment-emergent adverse event.
Source: Kappos et al. 2018;[3] Novartis Data on File (Clinical Study Report for Siponimod).[63]

Serious adverse events

Overall, [redacted] of patients had Grade 3/4 TEAEs ([redacted] siponimod, [redacted] placebo, Table 45).

Table 45: Patients with TEAEs, by maximum CTCAE grade

CTCAE Grade	Siponimod N=1,099, n (%)	Placebo N=546, n (%)
All Grades	[redacted]	[redacted]
Grades 3 and 4	[redacted]	[redacted]

A patient with multiple AEs with different CTCAE grades, is only counted under the maximum rating. A subject/AE with missing grade is still counted in the 'All grades' category.
Abbreviations: AE: adverse event; CTCAE: common terminology criteria for adverse events.
Source: Kappos et al. 2018;[3] Novartis Data on File (Clinical Study Report for Siponimod).[63]

TEAEs of Grade 3 or Grade 4 severity that were reported in 5 or more total patients included (siponimod, placebo):

[redacted]

[redacted]

Causality

TEAEs that were assessed by investigators as related to double-blind study drug were reported in a higher percentage of patients in the siponimod group than the placebo group ([redacted] and [redacted], respectively) (Table 46). [redacted] were the most common in the siponimod group; among these, [redacted].

Table 46: Patients with most frequently reported TEAEs related to study drug (at least 1.0% in the siponimod group)

Preferred Term	Siponimod N=1,099, n(%)	Placebo N=546, n(%)
Number of patients with at least one related TEAE	[redacted]	[redacted]
Headache	[redacted]	[redacted]
Bradycardia	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]
Alanine Aminotransferase Increased	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
Nausea	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]
Urinary Tract Infection	[redacted]	[redacted]
Gamma-Glutamyl Transferase Increased	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Herpes Zoster	[redacted]	[redacted]
Macular Oedema	[redacted]	[redacted]
Atrioventricular Block First Degree	[redacted]	[redacted]
Blood Pressure Increased	[redacted]	[redacted]
Oedema Peripheral	[redacted]	[redacted]
Upper Respiratory Tract Infection	[redacted]	[redacted]
Sinus Bradycardia	[redacted]	[redacted]
Hepatic Enzyme Increased	[redacted]	[redacted]

A patient with multiple occurrences of an AE or with multiple AEs within a preferred term is counted only once in this preferred term category.
Preferred terms are sorted in descending frequency of AEs in the siponimod column.
Abbreviations: AE: adverse event; TEAE: treatment-emergent adverse event.
Source: Kappos et al. 2018;[3] Novartis Data on File (Clinical Study Report for Siponimod).[63]

TEAEs leading to interruption or discontinuation of study treatment

TEAEs that led to temporary interruption of study drug occurred in a small percentage of patients: [redacted] in the siponimod group and [redacted] in the placebo group (Table 47). The most

common TEAEs leading to study drug interruption were [redacted].

Table 47: Patients with most frequently reported TEAEs leading to temporary interruption of study drug (at least 2 patients)

Preferred Term	Siponimod N=1,099, n(%)	Placebo N=546, n(%)
Number of patients with at least one TEAE leading to temporary interruption	[redacted]	[redacted]
Macular Oedema	[redacted]	[redacted]
Herpes Zoster	[redacted]	[redacted]
Alanine Aminotransferase Increased	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]
Carbon Monoxide Diffusing Capacity Decreased	[redacted]	[redacted]
Urinary Tract Infection	[redacted]	[redacted]
Appendicitis	[redacted]	[redacted]
Gastroenteritis	[redacted]	[redacted]
Headache	[redacted]	[redacted]
Malaise	[redacted]	[redacted]
Nausea	[redacted]	[redacted]
Seizure	[redacted]	[redacted]

A patient with multiple occurrences of an AE or with multiple AEs within a preferred term is counted only once in this preferred term category.
Preferred terms are sorted in descending frequency of AEs in the siponimod column.
Abbreviations: AE: adverse event; TEAE: treatment-emergent adverse event.
Source: Kappos et al. 2018;[3] Novartis Data on File (Clinical Study Report for Siponimod).[63]

TEAEs of grade 3/4 leading to temporary interruption in the siponimod group included [redacted].

A total of [redacted] of patients in the siponimod group and [redacted] in the placebo group had TEAEs leading to study drug discontinuation (Table 48). The most common of these were: macular oedema, alanine aminotransferase increased, and bradycardia. For the TEAEs occurring in at least two total patients, although some of these occurred in slightly higher percentages of patients randomised to siponimod than in the placebo group, the low incidences limit the utility of between-group comparisons. In the siponimod group, 3 patients discontinued study drug due to TEAEs of pulmonary function test decreased and two patients due to TEAEs of carbon monoxide diffusing capacity decreased.

Table 48: Patients with most frequently reported TEAEs causing permanent study drug discontinuation (at least 2 siponimod patients)

Preferred Term	Siponimod N=1,099, n(%)	Placebo N=546, n(%)
Number of patients with at least one TEAE leading to discontinuation	[redacted]	[redacted]
Macular Oedema*	[redacted]	[redacted]

Alanine Aminotransferase Increased	[redacted]	[redacted]
Bradycardia	[redacted]	[redacted]
Aspartate Aminotransferase Increased	[redacted]	[redacted]
Depression	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
Gamma-Glutamyl Transferase Increased	[redacted]	[redacted]
Pulmonary Function Test Decreased	[redacted]	[redacted]
Angina Pectoris	[redacted]	[redacted]
Atrioventricular Block First Degree	[redacted]	[redacted]
Atrioventricular Block Second Degree	[redacted]	[redacted]
Carbon Monoxide Diffusing Capacity Decreased	[redacted]	[redacted]
Hepatic Enzyme Increased	[redacted]	[redacted]
Malignant Melanoma in Situ	[redacted]	[redacted]
Oedema Peripheral	[redacted]	[redacted]
Seminoma	[redacted]	[redacted]
Uveitis	[redacted]	[redacted]

A patient with multiple occurrences of an AE or with multiple AEs within a preferred term is counted only once in this preferred term category.
Preferred terms are sorted in descending frequency of AEs in the siponimod column.
*One patient experienced macular oedema that was reported under a preferred term of cystoid macular oedema thus bringing the total number of macular oedema cases to 13 for all groups.
Abbreviations: AE: adverse event; TEAE: treatment-emergent adverse event.
Source: Kappos et al. 2018;[3] Novartis Data on File (Clinical Study Report for Siponimod).[63]

Patient deaths

A total of nine patient deaths were reported during the study, including one patient who died during screening (thus was not exposed to study drug). Details on the eight patients who died after randomisation are provided in Table 49.

Table 49: Details of patients who died

Primary preferred term (contributing)	Study Day relative to start date of study medication	Study Day relative to last date on [double-blind] study medication	Causality (per investigator)
Siponimod			
Completed suicide**	[redacted]	[redacted]	[redacted]
Urosepsis#	[redacted]	[redacted]	[redacted]
Septic shock§ (colon cancer Stage IV)	[redacted]	[redacted]	[redacted]
Malignant melanoma (multiple organ dysfunction syndrome)	[redacted]	[redacted]	[redacted]
Placebo			
Haemorrhagic stroke** (cardio-respiratory arrest)	[redacted]	[redacted]	[redacted]

Lung adenocarcinoma**	[redacted]	[redacted]	[redacted]
Death (unknown reason)	[redacted]	[redacted]	[redacted]
Gastric cancer**	[redacted]	[redacted]	[redacted]

Days from partial dates are based on imputed dates.
Event occurred after start of alternative MS DMT.
§ Event occurred 5 days after discontinuation from open-label siponimod.
* Causality not specified in listings.
** Deaths which occurred during double-blind study treatment until safety cut-off.
Source: Kappos et al. 2018;[3] Novartis Data on File (Clinical Study Report for Siponimod).[63]

In the siponimod group, 2 of the four deaths were due to infections (septic shock, urosepsis). For the patient who died due to septic shock, the patient's Stage IV colon cancer had started on Day 709 while the patient was receiving open-label siponimod. The death due to urosepsis occurred more than 10 weeks after discontinuation of siponimod, and after the patient had received two doses of rituximab. Death due to neoplasms was reported in 3 patients: 1 siponimod patient (malignant melanoma diagnosed on Day 120 while receiving double-blind siponimod) and 2 placebo patients (lung adenocarcinoma and gastric cancer).

For one patient in the placebo group, the cause of death was unknown and no information regarding the cause of death was available despite extensive follow-up.

B.2.10.3 Safety conclusions

Siponimod was generally well tolerated with a higher percentage of siponimod than placebo patients completing the Treatment Epoch (81.7% and 77.7%, respectively). Although there was no difference in the rate of infection AEs between the treatment groups, there was a slight increase in the rate of SAEs of infections on siponimod compared with placebo ([redacted] on siponimod vs [redacted] on placebo).

A higher proportion of patients treated with siponimod had AEs of macular oedema, hypertension, seizures/epileptic seizures, peripheral oedema or swelling and liver enzyme elevations compared with patients treated with placebo. However, no difference in the rate of deaths or malignancies between siponimod and placebo was observed.

Overall, siponimod was well tolerated, with an acceptable TEAE profile.

B.2.11 *Ongoing studies*

There are two ongoing studies for siponimod in people with SPMS:

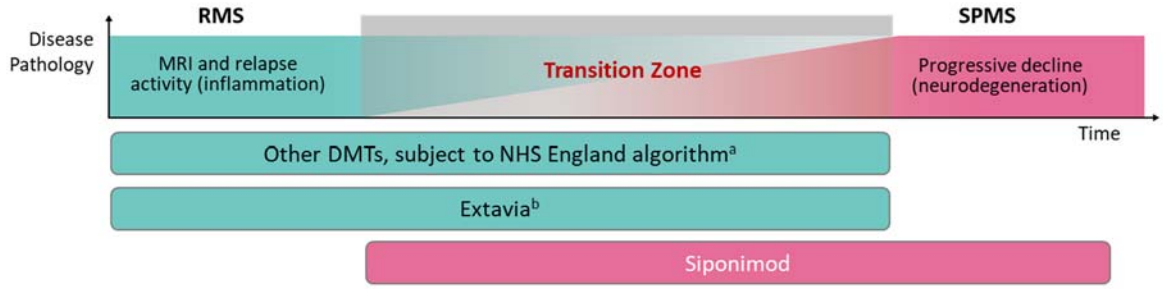
- The open-label extension part of the EXPAND trial; NCT01665144.[71]
- One phase III study: Safety and tolerability of conversion from oral or injectable DMTs to dose-titrated oral siponimod in advancing patients with RMS (EXCHANGE); NCT03623243.[91]

B.2.12 *Innovation*

SPMS is a typically hard-to-treat population, as demonstrated by some of the highly efficacious drugs licensed for RRMS (fingolimod and natalizumab) having failed in progressive MS trials (see Appendix D for further details on the numbers of failed or suspended trials in SPMS).[44, 62] None of the available DMTs in the UK have been shown to slow disability progression or

cognitive impairment in a representative population of patients with SPMS.[60, 92-94] Due to the lack of treatment options available for patients with SPMS, there is a strong clinical rationale for neurologists to avoid formal identification of SPMS in any patient currently receiving a DMT, due to the requirement to subsequently withdraw that patient from treatment (Figure 13).[14]

Figure 13: Current treatment options for patients with MS (replica of Figure 2)[51, 59]



All DMTs are limited to EDSS 6.5 due to lack of evidence at EDSS 7.0 or above.
[a] Approved DMTs: alemtuzumab; Avonex; cladribine; dimethyl fumarate; fingolimod; glatiramer acetate; natalizumab; ocrelizumab; Rebif; teriflunomide.
[b] Subject to relapse criteria.
Abbreviations: DMT: disease-modifying therapy; EDSS: Expanded Disability Status Score; MRI: magnetic resonance imaging; NHS: National Health Service; RMS: relapsing multiple sclerosis; SPMS: secondary progressive multiple sclerosis.

There are currently no licensed treatments available for patients with SPMS who do not experience relapses, and there is a significant unmet treatment need for these patients (Figure 13). Introduction of siponimod could create a step-change in the transition and management of SPMS in the NHS: research has revealed that clinicians believe that if a licensed and reimbursed DMT were to become available for SPMS, this would reduce the hesitancy of formally identifying SPMS in patients, and would give patients the option to switch to a DMT proven to be efficacious in SPMS.[14]

Given the evidence from the EXPAND trial, siponimod would be the first treatment to be recommended that can slow disability progression for patients with SPMS and the first for use in all patients with SPMS.

There are additional benefits of siponimod which are not captured within the quality-adjusted life-years (QALY) calculation, which is based upon EDSS progression and relapse. Siponimod had a benefit in improving cognitive processing speed in patients with SPMS as measured by SDMT (see section B.2.6.6). Qualitative studies have cited cognitive changes as one of the most challenging aspects of progressive MS. These 'invisible' changes affect both patients and caregivers, as low cognition has a substantial impact on social relationships and is often a barrier to patient self-management.[20, 95] Slower performances on SDMT correlate well with activities of daily living and also employment status; impaired performance on SDMT in patients with MS has been linked to decline in financial income, independently of physical disability.[96, 97] Siponimod may also have an impact on disability regression and relapse severity, which are not modelled in the economic analysis. Overall, these benefits to HRQoL are not captured within the QALY calculation.

Lastly, siponimod is orally administered, therefore avoiding the administration requirements of infusions or injections, and providing greater convenience to patients.

B.2.13 *Interpretation of clinical effectiveness and safety evidence*

B.2.13.1 Principal findings from the clinical evidence base

Siponimod provided clinically meaningful improvements in delaying the time to 3-month CDP in patients with SPMS.

The EXPAND trial enrolled 1,651 patients across 31 countries, with patients randomised 2:1 to siponimod or placebo. Results from the EXPAND trial demonstrated that treatment with siponimod was associated with a significant reduction in the time to 3-month CDP.

The EXPAND study achieved its primary endpoint by demonstrating a statistically significant improvement in time to 3-month CDP for siponimod, compared with placebo. This corresponded to a 21.2% risk reduction in EDSS progression for patients treated with siponimod compared with placebo (p=0.0134). Kaplan-Meier estimates indicated that the time to first quartile (25%) of patients experiencing 3-month CDP events was observed approximately 6 months later in patients randomised to siponimod compared with placebo. Improvements in time to disability progression have a meaningful impact on patients, maintaining their physical abilities for longer and extending the time before a patient progresses to reaching EDSS 7.0 and requires a wheelchair. A number of subgroups were analysed and reduction in the risk of disability progression with siponimod in these subgroups was consistent with the treatment effect observed in the overall population.

Additionally, a greater, and nominally significant, improvement was observed in the measure of time to 6-month CDP for siponimod, compared with placebo (25.9% risk reduction, p=0.0058, unadjusted for multiplicity), which is a more robust measure of CDP. The 6-month CDP outcome has consistently been preferred as a more robust measure of disability progression than 3-month CDP in previous appraisals in both relapsing and progressive forms of MS.[55, 56]

For the key secondary endpoints of the trial, siponimod provided a reduction in the volume of T2 lesions measured by MRI. Time to 3-month confirmed worsening in T25FW did not reach statistical significance, with an observed risk reduction of 6.2% in favour of siponimod. However, it is thought that T25FW may have suboptimal sensitivity for change in patients with more advanced MS (such as those in the EXPAND trial, with mean EDSS 5.4 at baseline),[3] as small increases in the EDSS can substantially affect their mobility.[3, 98] Nurses at a clinical advisory board organised by Novartis commented that the test may not be representative as it judges patients on just a single day, and it is not known how far the patient has already had to walk to the assessment centre. Additionally, patients often experience a high level of stress surrounding the test, which can lead to poor results. The reliability of this test is also affected by differences in test administration instructions (e.g. “static” vs “dynamic” start, “comfortable” vs “maximum, but safe” pace),[76] therefore it may not be the most appropriate measure for ambulatory performance.

Additional MRI-based analyses showed further benefits of siponimod. The proportion of patients free of T1 Gd-enhancing lesions was higher in patients receiving siponimod (89.4% vs 66.9%), as was the proportion of patients free of new or enlarging T2 lesions (56.9% vs 37.3%). Additionally, siponimod treatment resulted in a lower decrease in PBVC.

Siponimod showed a 55.5% rate reduction for confirmed relapses compared with placebo (ARR ratio 0.445, p<0.0001), and the time to first confirmed relapse showed a risk reduction of 46.4% that favoured siponimod (HR 0.54, p<0.0001).

Physical impact scores on the HRQoL measure MSIS-29 and the EQ-5D utility index scores showed [redacted], favouring siponimod. [redacted].

For cognitive measures, [redacted] were observed between siponimod and placebo in the comparison of adjusted mean change in correct responses on the SDMT. These [redacted] over time ([redacted]), demonstrating [redacted] in attention, concentration and processing speed for those taking siponimod compared with placebo. Additional cognitive tests of PASAT and BVMT-R were also used in EXPAND, but the results showed no significant difference between siponimod and placebo. However, in contrast to the SDMT measure, analyses based on a responder definition could not be conducted as there is no accepted measure of clinically meaningful change for PASAT and BVMT-R in MS; therefore, the clinical relevance of these results remains unclear.

In conclusion, the results presented demonstrate the clinical efficacy of siponimod in patients with SPMS, with a significant delay in disability progression, in terms of EDSS, and reduction in MRI and relapse activity. Approval of siponimod would allow patients who currently have no treatment options specifically approved for their phenotype to access a therapy that has been demonstrated to slow down the progression of their MS disease.

Siponimod provides even greater efficacy in the Active SPMS subgroup

[redacted] patients of the 1,651 patients in the trial were classified as having Active SPMS, as identified by the presence of relapses and/or MRI activity; to conduct this subgroup analysis in the EXPAND data set, relapses were defined as within the two years prior to the trial and MRI activity by the presence of gadolinium-enhancing T1 lesions at baseline. Within this *post hoc* subgroup, the EXPAND trial demonstrated an improvement in time to both 3- and 6-month CDP, and in both cases the effect size was [redacted] in the subgroup; [redacted] risk reduction in subgroup compared with 21.2% in total population for 3-month CDP and [redacted] compared with 25.9% for 6-month CDP.

Additionally, for the secondary endpoints of reducing ARR and delaying the time to first relapse, siponimod was [redacted] than placebo for both measures; [redacted] risk reduction in ARR and [redacted] in time to first relapse. These measures are arguably more important for this subgroup of patients than the average trial member due to their more frequent experience of relapses, displaying a benefit of siponimod for patients with Active SPMS.

The results of the matched adjusted treatment comparison support that siponimod is of benefit in treating patients with SPMS in comparison to interferons and natalizumab

Due to differences in patient populations, the amount of heterogeneity across the trials meant summary-level ITCs were not feasible for siponimod. However, by using a MAIC approach, it was still possible to compare siponimod with each comparator and determine differences in efficacy between the therapies.

Overall, in the separate analyses reflecting the various comparator trial SPMS populations, siponimod displayed favourable comparisons to all comparators, including natalizumab, for progression measures of 3- and 6-month CDP events.

Siponimod is associated with a manageable safety profile

The EXPAND trial showed siponimod to have a tolerable safety profile. The most common TEAEs (at least 10% of patients per group) were headache, nasopharyngitis, urinary tract infection, and fall.

B.2.13.2 Strengths and limitations of the evidence base

Internal validity of EXPAND

As discussed in Section B.2.5, the EXPAND trial was methodologically robust and well reported. The results were considered to be at low risk of bias:

- Participants were appropriately randomised using interactive response technology, treatment allocation was concealed, and participants and care providers were blinded
- The sample size was sufficient to detect a difference in the primary objective of time to three-month CDP between the two treatment groups
- Participant flow through the study was well reported, and there were no meaningful differences in the rates of treatment discontinuation between treatment arms
- All randomised patients were included in the efficacy analyses, thereby maintaining the principle of ITT analysis and preserving randomisation
- EDSS was measured by an Independent Rater every 3 months, to reduce potential bias of an investigator assessment

External validity

The results of the EXPAND trial can be generalised to the UK population, considering there was a high proportion of Caucasian patients, with 10 investigation sites in the UK.[63, 71] The trial was well designed with a low risk of bias. The results are also well aligned with the decision problem specified in the NICE scope.[1] The external validity of the EXPAND study is supported by the following:

- **Population** – The study population of EXPAND was defined as patients with SPMS. MS is usually diagnosed when patients are in their 20s–30s and later transition to the less inflammatory and more neurodegenerative SPMS phase. The patients had a mean age of 48 years and most patients were female (60.1%), reflective of the fact that MS is more common in women than men.[5] The EXPAND study population is relevant to the epidemiology of SPMS in the UK, and included patients from ten clinical trial sites across the UK. The majority of the study population were [redacted] which is in line with the majority White population in the UK (86.0%).[99]
- **Intervention** – Siponimod was directly evaluated as a treatment option for patients with SPMS, by comparing siponimod to placebo, facilitating indirect comparisons with relevant comparator DMTs

- **Comparators** – The efficacy and safety of siponimod was directly compared with that of placebo. The evidence presented in this submission (Section B.2.9) used a MAIC to compare siponimod with the comparators. Notably, the inappropriateness of a standard NMA has subsequently been supported by an independent study by ICER.[89]
- **Outcomes** – A wide range of outcomes were evaluated, including all outcomes outlined in the scope that are relevant to patients and to clinicians (CDP based on EDSS, MRI measures, relapse rates, functional and cognitive measures, HRQoL and safety). Time to 3- and 6-month CDP are particularly valuable endpoints for SPMS as there are currently no treatment options available to patients with SPMS that slow down disability progression

Limitations

- There has been no direct comparison of efficacy and safety between siponimod and the relevant comparators in a clinical trial setting, necessitating an indirect comparison to be performed. Due to population differences, high levels of heterogeneity, and an imbalance in treatment effect modifiers between trial populations, summary-level ITCs were deemed inappropriate and likely to be biased and MAICs had to be performed instead. Despite the caveat that not all differences could be accounted for, the anchored MAICs provide a more robust comparison option than summary-level ITCs would, making the best use of the available evidence.
- Due to uncertainty at the point of submission as to the final licenced population for siponimod, a specific subgroup population of Active SPMS is additionally presented. While the trial was not powered to detect a difference in 6-month CDP in this target subpopulation, nominal statistical significance was observed nonetheless.

B.2.13.3 Conclusion

The quality of the evidence provided by the EXPAND study is supported by robust and well-reported methodology, and the trial results are directly relevant to the treatment of patients with SPMS in NHS clinical practice. Siponimod improved the time to both 3-month and 6-month CDP compared with placebo in patients with SPMS, with a tolerable safety profile allowing for continued treatment. Combined with additional improvements in MRI measures and reductions in relapse rates, siponimod provides patients with a improvement in both disease and disability progression, particularly as there are currently no treatment options for these patients that have demonstrated to significantly slow disability progression in a typical SPMS population.

Additionally, results in the Active SPMS subgroup provided more favourable outcomes than for the ITT population for delaying disability progression.

The results of the MAICs consistently found siponimod to be superior ([redacted]) to comparators in their respective SPMS trial populations.

Siponimod offers patients with SPMS, clinicians, and the NHS a step-change in therapy, addressing for the first time their need for a DMT by offering them a treatment with proven efficacy on disability progression in SPMS.

B.3 Cost effectiveness

A *de novo* cost-utility analysis was undertaken based on a discrete-time cohort Markov model, similar to those used in previous NICE submissions for RRMS and PPMS.

- A *de novo* cost-utility analysis was undertaken based on a discrete-time cohort Markov model, similar to those used in previous NICE submissions for RRMS and PPMS. The model was based on 10 EDSS scores with 11 states (0 to 9 EDSS states and a 'Death' state or EDSS 10).
- The base-case analysis compared siponimod to Extavia®, the only current treatment option specifically reimbursed for patients with SPMS; however, Extavia® is only recommended for active disease evidenced by relapses. Due to the hesitancy of clinicians and the uncertainty in identifying SPMS, many patients remain on the DMT they were receiving for RRMS during the transition to SPMS. Siponimod is likely to displace these treatments, therefore comparisons to additional DMTs that are approved for RRMS are provided, where evidence permitted.
- The analysis was consistent with the NICE reference case: a cost-utility analysis with an NHS and Personal Social Services (PSS) perspective. Costs and benefits were discounted at a rate of 3.5% and a lifetime-equivalent time horizon was used.
- Clinical outcomes were based on the EXPAND trial, using 6-month CDP (or 3-month for comparisons where 6-month unavailable), and ARR data. Effectiveness estimates for comparisons were taken from the MAIC analysis (Section B.2.9.3); for DMTs without trials in SPMS, appropriate assumptions were tested in scenario analyses.
- Health state utilities were informed by EQ-5D-3L data collected directly during the EXPAND trial. Where data were not available for specific EDSS states, this was supplemented by data from Orme et al. Caregiver disutility values were obtained from the natalizumab NICE submission (TA127).
- Costs and healthcare resource use were captured in the analysis for drug acquisition, administration and monitoring costs; disease management and relapse costs; and AE management costs.

In the base case, using the with-Patient Access Scheme (PAS) price for siponimod and the with-PAS price for Extavia®, siponimod was associated with a pairwise ICER of £[redacted] per QALY gained vs Extavia®.

- Sensitivity analysis found the most influential parameters were the estimates of effectiveness on disability progression for each DMT. Other than disability progression, results were largely robust to parameter uncertainty with age, being the only other parameter that caused the ICER to cross the cost-effectiveness threshold. This demonstrates the stability of the model results to parameter uncertainty, other than relative effectiveness.
- Similarly, scenario analysis also found the ICER to be robust to the choice of parameter inputs.
- Probabilistic analysis found that even when the considerable parameter uncertainty in comparative effectiveness was taken into consideration, siponimod had a [redacted] probability of being the most cost-effective option at a willingness-to-pay threshold of £30,000/QALY. Given that Extavia® [redacted], other DMTs that may be displaced by siponimod.
- In scenario analyses considering other comparators beyond the base case, siponimod was cost-effective versus all considered comparators: IFNβ-1a (Avonex® and Rebif®), IFNβ-1b (Extavia®), glatiramer acetate, natalizumab, dimethyl fumarate, fingolimod, ocrelizumab, and teriflunomide.

B.3.1 *Published cost-effectiveness studies*

An SLR was conducted in November 2018 and updated in April 2019 to identify literature published on economic analyses of pharmacological interventions for the treatment of people with SPMS.

In total, five economic evaluations in SPMS were identified in the original economic SLR (Table 44). A total of 1,103 publications were excluded following full text review; the reasons for their exclusion are presented in Appendix G. No further publications reporting on economic evaluations in SPMS were identified in the SLR update; 26 publications were excluded.

Table 50: Publications reporting economic evaluations included in the original SLR (no further studies were identified in the SLR update)

	Author, year	Citation
1	Touchette 2003	Touchette DR, Durgin TL, Wanke LA, et al. 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;25:611-634.
2	Kobelt 2002	Kobelt G, Jönsson L, Miltenburger C, et al. Cost-utility analysis of interferon beta-1b in secondary progressive multiple sclerosis using natural history disease data. International Journal of Technology Assessment in Health Care 2002;18:127-138.
3	Kobelt 2000	Kobelt G, Jönsson L, Henriksson F, et al. Cost-utility analysis of interferon beta-1b in secondary progressive multiple sclerosis. International Journal of Technology Assessment in Health Care 2000;16:768-780.
4	Tappenden 2010	Tappenden P, Saccardi R, Confavreux C, et al. Autologous haematopoietic stem cell transplantation for secondary progressive multiple sclerosis: An exploratory cost-effectiveness analysis. Bone Marrow Transplantation 2010;45:1014-1021.
5	Forbes 1999	Forbes RB, Lees A, Waugh N, et al. Population based cost utility study of interferon beta-1b in secondary progressive multiple sclerosis. British Medical Journal 1999;319:1529-1533.

Abbreviations: SLR: systematic literature review.

Two economic evaluations may be relevant for the UK setting (Tappenden 2010, Forbes 1999), while the other three were not conducted in the UK. The results of all five identified studies and a critical appraisal of each economic evaluation is presented in Appendix G.

B.3.2 *Economic analysis*

Previous NICE appraisals in RRMS and PPMS informed the development of the economic model for this SPMS submission (TA32 [now superseded by TA527],[52] TA127,[100] TA254,[101] TA303,[102] TA312,[103] TA320,[104] TA441 [appraisal withdrawn],[105] TA493,[57] TA527,[52] TA533,[55] TA585[56]).

B.3.2.1 Patient population

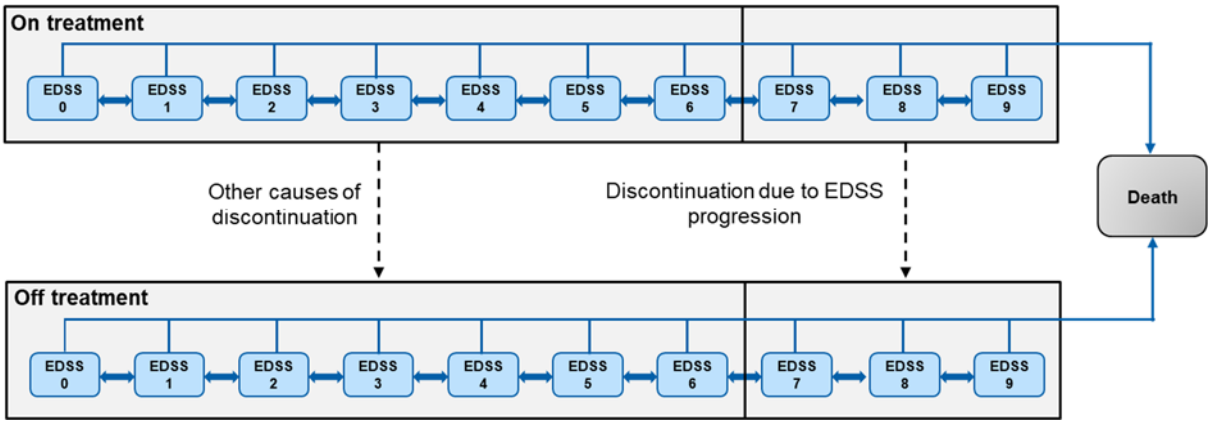
In line with the final NICE scope for this appraisal, and in line with the EXPAND trial, the patient population considered in the cost-effectiveness model was adult patients with SPMS, defined by a progressive increase in disability (of at least 6 months duration) in the absence of relapses or independent of relapses and those with an EDSS score of 3.0–6.5.[3, 9]

Additionally, a subgroup of patients with Active SPMS evidenced by relapse or imaging features was considered for the analysis using the EXPAND subgroup data presented in Section B.2.7.2 (for the subgroup of superimposed relapses in the two years prior to screening and/or presence of contrast-enhancing T1 lesions at baseline).

B.3.2.2 Model structure

A discrete-time cohort Markov model was employed to evaluate the cost-effectiveness of siponimod in patients with SPMS. The cycle length was 1 year, with a lifetime horizon. The model structure was based on 10 EDSS scores (where the half-point EDSS scores were rounded down and combined with the lower EDSS score, e.g. EDSS 4 comprised EDSS 4.0 and 4.5) with 11 states (0 to 9 EDSS states and a 'Death' state or EDSS 10) to accommodate differences in treatment practices, disability progression, cost of disease management, and quality of life; this was in line with the cost-effectiveness models that have been used in previous NICE technology appraisals.[56, 57] A schematic representation of the model is presented in Figure 14.

Figure 14: Cost-effectiveness model structure



Treatment is discontinued when a patient reaches EDSS 7.0 or above. EDSS 10 is equivalent to death due to MS, which is incorporated into the 'Death' state shown. Relapses are captured in the model as events rather than states.
Abbreviations: EDSS: Expanded Disability Status Scale.

A brief description of the model health states is presented below.

On-treatment

At the time of entry in the model, the cohort was classified into the EDSS states according to the baseline EDSS distribution as in the EXPAND clinical trial. Patients in this health state were assumed to be on-treatment and that they receive DMTs. During each cycle of the model, patients experience one of the following:

- Disability progression (move to higher EDSS state) or improvement in the disability status (move to lower EDSS state) or remain at their current level of disability (same EDSS state)
- Patients with EDSS scores ≥7 are discontinued from DMT administration owing to lack of evidence at EDSS 7.0 and above and are moved to the off-treatment group and receive best supportive care (BSC). The cut-off is chosen according to the Association of British Neurologists clinical guideline and the NHS England Commissioning Policy for DMTs in MS.[59, 106]
- Discontinuation due to any cause

- Relapse events
- AEs
- Mortality event and move to the death state

Off-treatment

Patients who discontinue treatment were assumed to retain the cumulative benefits of the DMT up to the point of discontinuation. On discontinuation, the patients were immediately switched to receive BSC, with progression and relapse rates based on the natural history model. No further treatment was administered. During each cycle of the model, patients may experience the following:

- Progress to higher EDSS states or lower EDSS states or remain at their current level of disability
- Relapse events
- Mortality event and move to the death state

Death

This is the absorbing state for the model. Patients can experience mortality from all states in the model.

Outcomes

Major outcomes considered in the model were disability progression (6-month CDP, or 3-month CDP where unavailable) and reduction in the frequency of relapses as assessed by the ARR. These outcomes were used to assign health state and relapse event-associated costs and utility values within the model. The primary endpoint in EXPAND was time to 3-month CDP, and secondary endpoints were 6-month CDP and reduction in the frequency of relapses.

Perspective

The base case analysis was performed from an NHS and PSS perspective.

Time horizon and cycle length

An annual cycle length was employed in the model, in line with previous MS HTA appraisals.[55, 103]

Lifetime horizon was considered as the base case in the model. Siponimod (or any other DMT) treatment benefits accrued in terms of lowering disability progression will have an impact on the associated events, i.e. survival and relapses. Therefore, considering the lifetime horizon in the model captures the full benefits of the treatment. The number of model cycles varies by chosen cohort starting age such that the model runs to the end of the national life tables at age 100.

Discounting

Discount rates of 3.5% were applied to both costs and benefits, in line with the NICE Methods Guide.[107]

A summary of the model characteristics is provided in Table 51. There are no previous appraisals in an SPMS patient population for comparison, therefore Table 51 compares the economic model in this submission to the two recent MS submissions for ocrelizumab, in RRMS,[55] and PPMS.[56]

Table 51: Features of the economic analysis

Factor	Previous appraisals		Current appraisal (SPMS)	
	TA533 (RRMS)[55]	TA585 (PPMS)[56]	Chosen values	Justification
Time horizon	50 years	50 years	Lifetime – number of model cycles varies by chosen cohort starting age such that the model runs to the end of the national life tables at age 100 (Section B.3.2.2)	SPMS is a lifelong condition.
Source of natural history EDSS	British Columbia	MSBase	EXPAND trial data, supplemented by the London Ontario database (Section B.3.3.2)	EXPAND data are the only recent data available for patients with SPMS. The London Ontario database has been used in previous NICE MS appraisals, and provides separate data for RRMS and SPMS.
Source of natural history relapse	Patzold et al. 1982,[108] combined with UK MS survey data	MSBase	EXPAND trial data, supplemented by Patzold et al. 1982,[108] and UK MS survey (Section B.3.3.3)	EXPAND data are the only recent data available for patients with SPMS. Patzold et al. has been used in previous NICE MS appraisals.
Source of MS mortality multiplier	Pokorski et al. 1997,[109] extrapolated for EDSS states	Pokorski et al. 1997,[109] extrapolated for EDSS states	Pokorski et al. 1997,[109] extrapolated for EDSS states (Section B.3.3.4)	Consistent with previous NICE MS appraisals.
Application of treatment effect	ARR 12-week CDP (at submission) SPMS transition (50%)	24-week CDP 9-HPT MFIS	6-month CDP ARR (Sections B.3.3.2 and B.3.3.3)	6-month CDP was a key secondary endpoint of the EXPAND trial, and has been preferred over 3-month CDP by NICE committees in previous MS appraisals.
Treatment effect waning	Not applied – all-cause treatment discontinuation acts as a proxy for waning	Arbitrary treatment waning effect from 10 years	Not applied – all-cause treatment discontinuation acts as a proxy for waning	Consistent with TA533 in which the Committee accepted that treatment stopping could be considered a proxy for treatment waning in the absence of evidence.[55]
Application of treatment discontinuation	Trial data (all-cause discontinuation)	Trial data (all-cause discontinuation)	EXPAND trial data (all-cause discontinuation) (Section B.3.3.5)	Consistent with previous NICE MS appraisals.
Stopping rule	EDSS ≥7.0	EDSS ≥7.0	EDSS ≥7.0 (Section B.3.2.2)	ABN clinical guideline recommends treatment

	SPMS transition			to stop once patients are non-ambulatory.[106]
Source of patient utilities	Trial data and Orme et al. 2007[17]	Trail data and Orme et al. 2007[110]	EXPAND trial data, supplemented by Orme et al. 2007[17] (Section B.3.4.1)	EXPAND data are the only recent data available for patients with SPMS but do not cover all EDSS states. Orme et al. 2007[17] has been used in previous NICE MS appraisals.
Source of relapse disutility	Orme et al. 2007[17]	Orme et al. 2007[17]	EXPAND trial data (Section B.3.4.1)	EXPAND data are the only recent data available for patients with SPMS.
Source of caregiver disutility	Loveman et al. 2006 and UK MS survey data	NICE natalizumab submission [TA127]	NICE natalizumab submission [TA127] (Section B.3.4.1)	Consistent with previous NICE MS appraisals.[100]
Source of EDSS cost	UK MS survey data	UK MS survey data	UK MS survey data	Consistent with previous NICE MS appraisals.[104]
Source of relapse cost	Tyas et al. 2007	Tyas et al. 2007	RSS model and ScHARR analysis	Consistent with recent NICE MTA in MS (TA527).[52]

Abbreviations: 9-HPT: nine-hole peg test; ABN: Association of British Neurologists; ARR: annualised relapse rate; CDP: confirmed disability progression; EDSS: Expanded Disability Status Scale; MFIS: modified fatigue impact scale; MS: multiple sclerosis; MTA: multiple technology assessment; PPMS: primary progressive multiple sclerosis; RRMS: relapsing-remitting multiple sclerosis; RSS: risk sharing scheme; ScHARR: School of Health and Related Research; SPMS: secondary progressive multiple sclerosis.

B.3.2.3 Intervention technology and comparators

The base case comparator was considered to be Extavia® (Interferon β-1b), which is the only current treatment option for patients with SPMS but is only recommended in the case of patients experiencing continuing relapses.[52]

However, due to the hesitancy and uncertainly in identifying SPMS (as described in Section B.1.3.3), clinicians reported that many patients stay on the DMT they were receiving for RRMS through the transition phase to SPMS and it is expected that, if approved, siponimod would displace these treatments.[14] Therefore, the model includes other DMTs that are approved for RRMS as comparators in the cost-effectiveness analysis, comprising:

- Dimethyl fumarate (DMF)
- Fingolimod
- Glatiramer Acetate (GA)
- Interferon β-1a (Avonex®)
- Interferon β-1a (Rebif® 44 and 22)
- Natalizumab
- Ocrelizumab
- Teriflunomide

As noted in Section B.1.3.3, although DMTs for RRMS have not been proven to be effective in SPMS, continuing the DMT is preferred over being left with symptomatic treatment only.[14, 60] The

introduction of siponimod would remove the hesitancy for SPMS to be identified in these patients at a much earlier stage and to allow them continued treatment with a DMT proven to be effective for their MS phenotype. In addition, based on the NHS England treatment algorithm, patients below EDSS 6 are currently unlikely to meet the stopping criterion for RRMS DMTs even if they exhibit signs of SPMS: “Secondary progressive disease would usually only be diagnosed in patients with an EDSS of 6.0 or greater”.[59] Also based on the NHS England treatment algorithm, the SPMS stopping criterion for RRMS DMTs only applies in patients with “absence of relapse activity”, thereby anticipating that patients with Active SPMS remain on DMT treatment unless another stopping criterion, such as progressing to EDSS 7, applies.[59] As such, siponimod is expected to displace current DMT usage in NHS patients in line with its full anticipated license.

Two further DMTs currently approved by NICE for use in some forms of RRMS were not considered comparators: cladribine and alemtuzumab. Both DMTs are induction therapies given for an initial course rather than ongoing treatments. Patients treated with either DMT who begin to transition to SPMS will be exhibiting treatment failure of the induction therapy, but this is not considered likely to occur during the initial two-year treatment stage and therefore these DMTs are unlikely to be displaced by siponimod. Furthermore, at the present time, alemtuzumab is the subject of an EMA restriction pending further safety considerations, and should only be started in adults with RRMS that is highly active despite treatment with two DMTs or where other DMTs cannot be used.[111]

Discontinuation Rule

The Association of British Neurologists (ABN) clinical guideline and the NHS England Treatment Algorithm for MS DMTs state that treatment should be stopped if the patient has developed an inability to walk (EDSS 7.0), which is persistent for more than 6 months due to MS.[59, 106] The economic analysis therefore applies a stopping rule at EDSS 7.0 (patients restricted to wheelchair).

B.3.3 *Clinical parameters and variables*

Whenever possible, patient-level data from the EXPAND study were used to inform clinical parameters and variables in the economic analysis. Further information regarding this trial is presented in depth in Section B.2.3 and Appendix L.

B.3.3.1 Baseline Patient Characteristics

The baseline input parameters for defining patient characteristics considered in the model are described in Table 52. These parameters determine the baseline risk of the cohort.

The baseline mean age of the cohort was estimated from the pooled patients in the siponimod and placebo arms of the EXPAND trial at the beginning of the study.

The percentage of male patients in the cohort was calculated from data from the EXPAND trial. This input accounts for the difference in generalised mortality based on gender.

The initial EDSS distribution of the population used in the model was estimated from patients from both arms (siponimod and placebo) in the EXPAND trial. The proportion of patients in each EDSS state was adjusted to a cohort size of 1,000.

Table 52: Patients Characteristics Used in the Model

Characteristic	ITT population	Active SPMS
Mean age (in years)	48	[redacted]
% male patients	39.9%	[redacted]
Baseline EDSS distribution in percentages (assuming cohort size of 1,000 patients)		
EDSS 0	0%	0.00%
EDSS 1	0%	0.00%
EDSS 2	[redacted]	[redacted]
EDSS 3	[redacted]	[redacted]
EDSS 4	[redacted]	[redacted]
EDSS 5	16.09%	[redacted]
EDSS 6	55.33%	[redacted]
EDSS 7	[redacted]	[redacted]
EDSS 8	0%	0.00%
EDSS 9	0%	0.00%
Total	**100%**	**100%**

Abbreviations: EDSS: Expanded Disability Status Scale; ITT: intention-to-treat; SPMS: secondary progressive multiple sclerosis.
Source: EXPAND trial.[3]

B.3.3.2 Disability Progression

The transition of patients between each of the EDSS states was modelled using natural history data. Treatment benefits (HRs for disability progression) were applied to the natural history disability progression transition matrix to estimate the disability progression of patients on DMT. The natural history source for the transition matrix was assumed to be the same for all subgroups considered in the model, due to a lack of subgroup-specific natural history data.

Limited information was available in the literature on the natural history disability progression for patients with SPMS. The following sources were considered:

EXPAND placebo-arm data

The EXPAND placebo-arm data were the only recent data source available for patients with SPMS. The EXPAND trial included 546 patients in the placebo arm with an EDSS score of 3.0 to 6.5, for up to 3 years. In line with the natalizumab NICE manufacturer submission,[100] a multi-state-modelling (MSM) approach was used to derive the transition probability matrix from the placebo-arm data of EXPAND. However, the EXPAND placebo arm did not have all EDSS transitions.

London Ontario database

The London Ontario dataset is well established and has been used extensively in previous NICE MS submissions (Appendix M).[55] While the data from London Ontario have been criticised in previous appraisals, it provides separate natural history transitions for RRMS and SPMS.

British Columbia database

The British Columbia database has been commonly used in the latest NICE HTA submissions in MS and is relatively more recent and complete, but it was not considered as the base case

because the British Columbia dataset does not differentiate between patients with RRMS and those with SPMS (Appendix M).[112]

Overall, the natural history disability progression from the EXPAND placebo arm was considered as the base case. The transitions that were not available in the EXPAND placebo arm were taken from the London Ontario database. A detailed explanation on the MSM approach and the method used to pool data from the London Ontario database are presented in Appendix M. The overall transition probability matrix for disability progression used in the model is shown in Table 53.

Table 53: Transition matrix (normalised to 1) from EXPAND placebo arm (MSM approach) and London Ontario database for SPMS to SPMS transition

From/to	0	1	2	3	4	5	6	7	8	9	10
0	1.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
1	0.000	1.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
2	0.000	0.000	0.455	0.375	0.099	0.041	0.027	0.002	0.000	0.000	0.000
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.002	0.000	0.000
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.006	0.000	0.000
5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.023	0.000	0.000
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.048	0.000	0.000
7	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.644	0.349	0.006	0.000
8	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.991	0.008	0.000
9	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	1.000	0.000
10	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	1.000

EDSS 3–6 are sourced from the EXPAND placebo arm and EDSS 0–2 and 7–10 are sourced from the London Ontario database.
Abbreviations: MSM: multi-state modelling; SPMS: secondary progressive multiple sclerosis.

The effects of treatment are applied in the model by applying the HR to the natural history disability progression transition probability matrix. Treatment transition probabilities, *pt*, for patients receiving each DMT were calculated by applying the relative effect of treatment, *r*, to the underlying natural history transition probabilities, *pn*, where progression had occurred (e.g. from EDSS 4 to EDSS 5).

$$pt = 1 - exp(-(-(ln(1 - pn))r))$$

The probability of a patient staying in the same EDSS state was calculated as 1 minus the probability of progressing to higher EDSS states. The relative treatment effect was only applied to forward transition probabilities and not to backward transitions (i.e. EDSS improvements only). In this approach, 6-month CDP was considered as the base case model since it is not impacted by relapse, as suggested by the NICE appraisal committee during TA533.[55] However, for some comparators only 3-month CDP data were available, and in these cases the 6-month CDP data available for Extavia were used instead of less robust 3-month CDP data; assuming a single efficacy value for all interferons is aligned with the recent NICE multiple technology assessment (MTA), TA527.

HRs for 6-month CDP were available from the MAIC analysis (Section B.2.9). Considering that a limited number of DMTs for SPMS have been evaluated in clinical trials, HRs from the MAIC analysis were only available for certain comparators: results of the MAIC analyses used in the

model are presented in Table 54. For the rest of the comparator DMTs, assumptions had to be made.

Table 54: Effectiveness estimates for time to 6-month CDP in patients with SPMS from the MAIC analysis used in the model

Comparator	Comparator DMT vs placebo EE (95% CI)	Siponimod vs placebo EE (95% CI)	Source
Interferon β-1b (Extavia®)	0.92 (0.71–1.20)#	[redacted]	MAIC of North American Study and EXPAND
Natalizumab (Tysabri®)	1.06 (0.74–1.53)*	[redacted]	MAIC of ASCEND and EXPAND

#effect estimates are HRs and the outcome is time to 6-month CDP
*effect estimates are odds ratios and the outcome is proportion with 6-month CDP at 96 weeks
Abbreviations: CDP: confirmed disability progression; CI: confidence interval; DMT: disease-modifying therapy; EE: effect estimate; HR: hazard ratio; MAIC: matching-adjusted indirect comparison; SPMS: secondary progressive multiple sclerosis.

For natalizumab, time to 6-month CDP data were not available from the ASCEND trial. Therefore, the proportion of patients with 6-month CDP at 96 weeks was used for the MAIC analysis, as reported in Section B.2.7.2. In order to include the natalizumab trial in the economic model the relative effectiveness for this outcome was assumed to be interchangeable with relative effectiveness on the time to 6-month CDP at 96 weeks and these data were used in the model.

As noted in Section B.2.7.2, separate MAIC analyses were not feasible for the Active SPMS subgroup. Effectiveness estimates for subgroups for comparators were assumed to be the same as in all patients with SPMS (ITT).

B.3.3.3 Relapse Events

Relapse events were expressed in terms of ARR. Treatment benefits (relative risk [RR] for relapse efficacy) were applied on the natural history ARR to estimate the frequency of relapses experienced by the patients on DMTs.

Analysis of natural history relapse rates by EDSS health states is the most commonly used approach in previous NICE appraisals.[55, 103] This approach was considered in the base case analysis of the model.

Natural history ARR data were assessed from the placebo arm of the EXPAND clinical trial and a study by Patzold and Pocklington (1982).[108] Natural history ARR for all possible EDSS states was not available from the EXPAND trial. Therefore, the ARR for EDSS 3–7 was obtained from EXPAND (ARR for EDSS 8 and 9 was assumed to be the same as that for EDSS 7) and the ARR for EDSS 0–2 was obtained from the study by Patzold and Pocklington and multiplying the value with the EDSS distribution from the UK MS survey to derive the ARR per EDSS state.[17, 108] The values utilised in the model are presented in Table 55.

Table 55: Natural history ARR used in the model

EDSS	EXPAND, Patzold and Pocklington 1982 and UK MS survey	
	ITT*	Active SPMS*
0	0.000	0.000

1	0.000	0.000
2	0.465	0.465
3	[redacted]	[redacted]
4	[redacted]	[redacted]
5	[redacted]	[redacted]
6	[redacted]	[redacted]
7	[redacted]	[redacted]
8	[redacted]	[redacted]
9	[redacted]	[redacted]
10	0.000	0.000

*ARR for EDSS 3–7 is taken from the EXPAND trial[3] (ARR for EDSS 8 and 9 assume the same value as for EDSS 7), and ARR for EDSS 0–2 is taken from Patzold et al.[108] and the UK MS survey.[17]
NB. model states EDSS 0 and 1 are unused in practice and very few of the cohort start in or regress to EDSS 2.
Abbreviations: ARR: annualised relapse rate; EDSS: Expanded Disability Status Scale; ITT: intention-to-treat; MS: multiple sclerosis; SPMS: secondary progressive multiple sclerosis.

Relapse Severity

The proportion of relapses requiring hospitalisation and those not requiring hospitalisation for both siponimod and BSC were estimated from the EXPAND trial. Data analysis from EXPAND revealed that [redacted] of relapses did not require hospitalisation, whereas [redacted] of relapses required hospitalisation. Due to the lack of information specifically for the effectiveness of DMTs on relapse severity in SPMS, this was assumed to be the same for all comparator DMTs as for siponimod, in line with assumptions in previous models.[100, 101]

Relapse Duration

The health effects of relapses were measured as QALY losses and were calculated from the mean duration of each relapse event multiplied by the loss in the utility associated with each relapse.

The mean duration of each relapse event was obtained from the EXPAND trial. The relapse data are summarised according to the requirement for hospitalisation and are pooled across the treatment groups (siponimod and placebo) in the EXPAND trial (Table 56).

Table 56: Relapse event duration (in days) and hospitalisation status

Relapse event type	Duration (days)	Source
Relapse requiring hospitalisation	[redacted]	EXPAND trial (pooled analysis of patients in siponimod and placebo arms)
Relapse not requiring hospitalisation	[redacted]	

Relapse Effectiveness

The effects of the treatment are applied in the model by applying the RR to the natural history ARR to yield a treatment relapse rate per annum per patient. The RR for relapse rate (ARR) was available from the MAIC analysis (Section B.2.9). The results of the MAIC and non-MAIC analyses used in the model are presented in Table 57.

Table 57: Effectiveness estimates (relative risk) for annualised relapse rate in patients with SPMS used in the model

Comparator	Comparator DMT vs placebo RR (95% CI)	Siponimod vs placebo RR (95% CI)	Source
Interferon β-1b (Extavia®)	0.65 (0.48–0.88)	[redacted]	MAIC - EXPAND & North American Study & European Study
Interferon β-1a (Rebif® 22 µg)	0.69 (0.56–0.84)	[redacted]	MAIC - EXPAND & SPECTRIMS
Interferon β-1a (Rebif® 44 µg)	0.69 (0.56–0.85)	[redacted]	MAIC - EXPAND & SPECTRIMS
Natalizumab (Tysabri®)	0.45 (0.32–0.63)	[redacted]	MAIC - EXPAND & ASCEND
Interferon β-1a (Avonex®)	0.67 (0.49–0.90)	[redacted]	MAIC - EXPAND & IMPACT
Siponimod	-	0.45 (0.34; 0.59)	EXPAND

Abbreviations: CI: confidence interval; DMT: disease-modifying therapy; MAIC: matching-adjusted indirect comparison; RR: relative risk; SPMS: secondary progressive multiple sclerosis.

B.3.3.4 Mortality

The probability of death was considered as a function of time to account for the increasing risk of death associated with the increasing age of the cohort over time. The annual probability of death was derived in two steps:

- A gender-averaged all-cause mortality rate was derived from the Office for National Statistics (ONS) 2015–2017[113]
- The mortality rate was calculated for the excess mortality risk for SPMS using published standardised mortality ratios comparing mortality in patients with SPMS vs the general population

In general, MS is not a fatal disease, and premature death of patients with SPMS is most likely due to disease complications, such as infections and respiratory diseases, or other comorbidities, which may occur during the disease course.[114]

General population all-cause mortality was considered from the England and Wales Life Tables from the ONS.[113] The percentage of male patients in the model was considered from the baseline characteristics of the EXPAND trial.

There is no evidence that quantifies the excess mortality risk in patients with SPMS alone. It was assumed that excess mortality risk in patients with MS is not directly related to phenotype, such as SPMS, independently and so generalised excess mortality rates reported for MS were used.

An EDSS-dependent mortality multiplier was considered as the base case approach as studies show that risk of mortality increases as the EDSS score progresses in patients with MS.[109, 115]

The EDSS-dependent mortality multiplier derived from the study by Pokorski et al. 1997 was used as the base case.[109] Pokorski data have been widely used and consistently accepted in previous MS NICE appraisals. Although the data are considered to be outdated from a period

prior to improvements in MS care, this approach was considered to be the most clinically plausible, despite its limitations, in the recent MTA TA527.[52] The mortality multipliers used in the model are presented in Table 58.

Table 58: Mortality multiplier estimation used in the model

EDSS	0	1	2	3	4	5	6	7	8	9
Pokorski 1997 (Base case)	1	1.4316	1.6002	1.6372	1.6740	1.8420	2.2726	3.0972	4.4472	6.4540

Abbreviations: EDSS: Expanded Disability Status Scale.

B.3.3.5 Treatment Discontinuation

All-cause discontinuation considered in the cost-effectiveness model includes withdrawal due to AEs or lack of effectiveness. Discontinuation rates were applied on an annual basis in line with the cycle length of the model. Patients discontinuing DMTs were assumed to then receive BSC. The all-cause discontinuation rate was applied in a time-dependent manner in the base case.

Discontinuation rates were based on time and were obtained from the EXPAND trial, which was the primary source of data on all-cause discontinuation of treatment. Different distributions were fitted to the data to estimate the proportion of patients who discontinued beyond the trial duration. Based on the model fit, the Akaike information criterion (AIC) statistic and visual inspection, the exponential and Weibull functions were the most appropriate fit to the data. Of these, the Weibull was chosen as the exponential exhibited unrealistically high continuation rates at later timepoints (Figure 15). Parameters used to fit the distribution are shown in Table 59.

MAICs for discontinuation outcomes were explored in the feasibility assessment (Section B.2.9.2), but treatment effect modifiers related to adverse events and discontinuation were not well reported in comparator studies, thereby precluding a valid MAIC.

Discontinuation rates for the comparator DMTs were obtained by applying the relative risk from a discontinuation Bucher ITC (see details in Appendix M) to the discontinuation rate of siponimod obtained from the parametric curve for the respective year (see Table 60 below for comparator discontinuation relative risks).

Figure 15: Weibull distribution fitted to discontinuation data

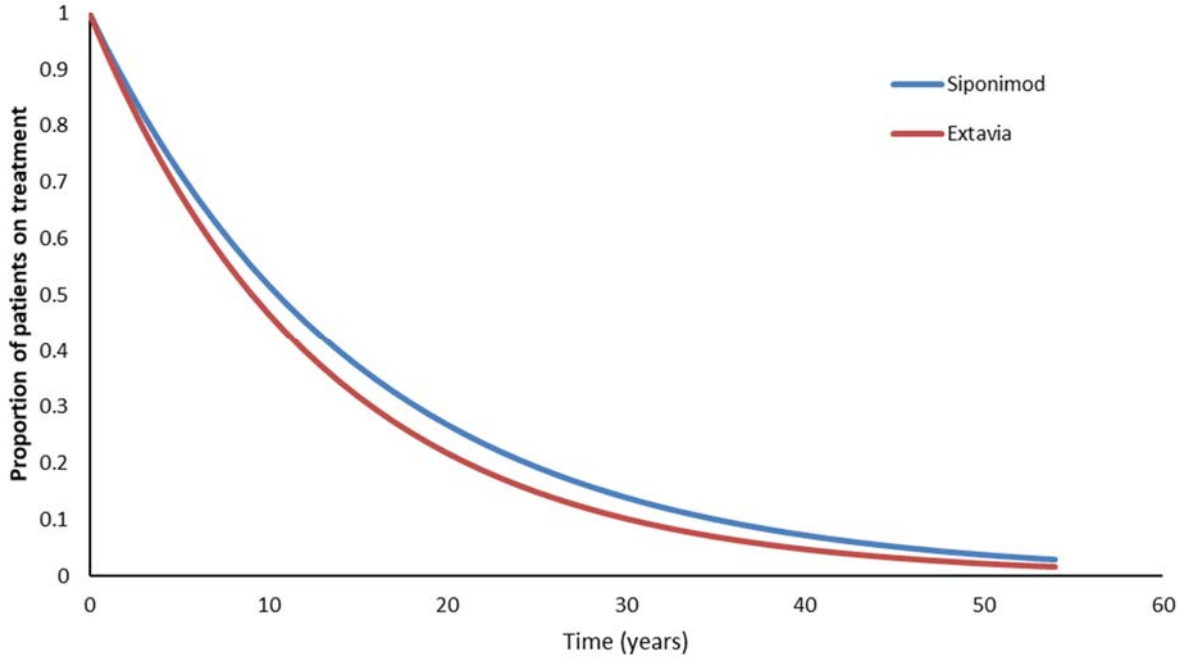


Table 59: Parametric distribution statistics for all cause discontinuation from EXPAND

Distribution	AIC	Scale	Shape
Exponential	1292	0.104511	-
Weibull	1294	9.46475	1.00672
Log-logistic	1294	0.1115588	1.063823
Log-normal	1298	2.435424	1.959851
Gompertz	1294	-0.037	0.10837

Abbreviations: AIC: Akaike information criterion.

Scenario Analysis

In an alternative scenario, the all-cause discontinuation rate was applied in a time-constant manner.

The annual discontinuation probabilities were assumed to be constant and were applied to each year of the model time horizon. The ITC used in the base case was again used as the source for all-cause discontinuation of treatment. The output of the ITC for treatment discontinuation is represented as relative risk of discontinuation for siponimod vs comparator DMT (Table 60). The following process was used to generate annual probabilities of discontinuation for each treatment:

- Baseline discontinuation probability for siponimod
    - As a reference point, the probability of withdrawal from siponimod was obtained from the EXPAND trial: 197 out of 1,100 patients treated with siponimod discontinued the study drug by the end of the 3-year controlled period (17.91% discontinuation probability) (see details in Appendix M)

- Convert 3-year discontinuation probability to annual probability (6.37% annual discontinuation probability)

- Apply the relative treatment relative risk (siponimod vs comparator DMT) to the annual discontinuation probability of siponimod

The time-constant discontinuation probabilities used in the model are shown in Table 60. Details of the ITC are given in Appendix M.

Table 60: Time-constant discontinuation probabilities used in the model

DMT	Relative risk (Siponimod vs comparator DMT)	Annual discontinuation probability calculation	Annual discontinuation probability	Source
Siponimod	N/A	6.37%	6.37%	EXPAND
Natalizumab (Tysabri)	[redacted]	= 6.37% / [redacted]	[redacted]	ASCEND
Interferon β-1a (Rebif® 22 µg)	[redacted]	= 6.37% / [redacted]	[redacted]	SPECTRIMS
Interferon β-1a (Rebif® 44 µg)	[redacted]	= 6.37% / [redacted]	[redacted]	SPECTRIMS
Interferon β-1b (Extavia®)	[redacted]	= 6.37% / [redacted]	[redacted]	North American Study European Study
Interferon β-1a (Avonex®)	[redacted]	= 6.37% / [redacted]	[redacted]	IMPACT

Abbreviations: DMT: disease-modifying therapy; N/A: not applicable.

B.3.3.6 Safety

TA533 included AEs reported in '≥5% of patients by preferred term' in the controlled treatment arm.[55] For the base case scenario, the same criteria as reported in TA533 was employed for considering AEs from the EXPAND trial for siponimod (Table 61). For other DMTs, we assumed the same criteria as reported for patients with RRMS and TA533 (Table 62) or considered from individual SPMS trials.[55] Alternatively, for the scenario analysis, AEs for the DMTs were considered from the respective appraisals, however the base case approach was preferred due to the recency of the appraisal (TA533; Appendix M).

Table 61: Adverse events (with >5% during trial period in any arm of trial) of siponimod from EXPAND trial

Adverse event	3-year probability	Annual probability
Headache	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]
Fall	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]

Upper respiratory tract infection	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]
Nausea	[redacted]	[redacted]
Influenza	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Back pain	[redacted]	[redacted]
Alanine aminotransferase level increased	[redacted]	[redacted]
Pain in extremity	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]
Depression	[redacted]	[redacted]

Table 62: Annual adverse event probability (in %) for DMTs considered from ocrelizumab RRMS NICE submission

Adverse event	DMF	FING	GA	AVO	REB22	REB44	EXT	NAT	OCR	TERI
Arthralgia	-	3.50	5.10	3.80	6.20	6.20	7.20	10	2.30	-
Back pain	5.40	5.50	5.00	4.10	4.50	4.50	6.00	-	5.20	5.30
Bronchitis	-	4.20	-	2.30	3.50	3.50	-	-	5.10	-
Depression	3.70	4.30	5.30	7.50	6.50	6.50	9.00	10	13.10	-
Fatigue	5.70	8.10	8.40	10.30	7.70	7.70	13.10	14.50	12.00	6.40
Headache	8.20	16.60	9.70	15.00	15.00	15.00	16.90	21.20	7.70	11.30
Influenza-like illness	-	3.50	-	24.40	21.40	21.40	-	-	2.60	-
Infusion related reaction	-	-	-	-	9.70	9.70	-	-	34.30	-
Injection site pain	-	-	15.60	5.00	20.80	20.80	4.30	-	0.40	-
Insomnia	-	-	-	-	4.60	4.60	-	-	5.60	-
Nasopharyngitis	9.80	16.10	9.40	13.30	10.20	10.20	9.60	-	10.80	13.30
PML	-	-	-	-	-	-	-	2.10	-	-
Sinusitis	-	-	-	-	5.40	5.40	-	-	5.60	-
URI	5.60	16.60	4.70	6.10	10.50	10.50	4.50	-	6.40	-
UTI	8.20	5.90	5.20	4.90	12.10	12.10	5.30	10.50	3.10	3.60

All values are in %.
Abbreviations: AVO: Avonex; DMF: dimethyl fumarate; DMT: disease-modifying therapy; FING: fingolimod; GA: glatiramer acetate; EXT: Extavia; NAT: natalizumab; OCR: ocrelizumab; PML: progressive multifocal leukoencephalopathy; REB22: Rebif 22 µg; REB44: Rebif 44 µg; RRMS: relapsing-remitting multiple sclerosis; TERI: teriflunomide URI: upper respiratory tract infection; UTI: urinary tract infection.

B.3.4 *Measurement and valuation of health effects*

Health state utilities (HSUs) from EXPAND combined with a study by Orme et al. were considered as the base case model inputs.[17] HSUs from EXPAND data are the most recent data in confirmed patients with SPMS. However, HSUs for all EDSS states were not available from EXPAND. Therefore, data from the study by Orme et al. were used for data lacking from EXPAND. Orme et al. was identified from an SLR (see Section B.3.4.3 for more details), reporting HSU values specific for SPMS from a UK patient sample and using the UK value set.

B.3.4.1 Health-related quality of life data from clinical trials

Estimation of health state utilities from EXPAND quality of life data

HSUs derived from EXPAND are presented in Table 63. Health-related quality of life data were collected using the EQ-5D-3L questionnaire in the EXPAND trial, which was consistent with the NICE reference case.

Previous appraisals, such as the natalizumab and ocrelizumab RRMS appraisals assessed EQ-5D scores by linking them with EDSS states using a regression analysis in alignment with the methodology used in literature (Orme et al.).[17, 55, 100] These appraisals determined that age, gender, EDSS state, number of years since diagnosis and relapse occurrence all demonstrated important associations with utilities in terms of magnitude and significance of effect. A repeated measures linear regression was undertaken using these variables to evaluate health-state utilities based on the EXPAND HRQoL data. The detailed method used for the regression analysis is presented in Appendix M.

There were few patients with EDSS states 0, 1, 2, 8 and 9. The distribution of EDSS states during the EXPAND study ranged from 2 to 8. However, EQ-5D data for EDSS states 2 and 8 were associated with considerable uncertainty due to the small number of observations at these states. Therefore, HSUs derived from regression analysis for these states were not reliable or available. For EDSS states 3 to 7 HSUs were taken from EXPAND and for rest of the EDSS states (EDSS 0, 1, 2, 8 and 9) SPMS-specific HSUs were considered from Orme at al. (see below). These utility values are presented in Table 63.

Table 63: Health state utilities derived from EXPAND trial

EDSS	Utilities from EXPAND and Orme et al. (Base case)
0	0.825
1	0.754
2	0.660
3	[redacted]
4	[redacted]
5	[redacted]
6	[redacted]
7	[redacted]
8	−0.094
9	−0.240
10	0

Abbreviations: EDSS: Expanded Disability Status Scale.

Estimation of health state utilities from other sources considered in the model

HSUs derived from the study by Orme et al. are presented in Table 64. The HSUs were derived by applying the reported disutility weights (a fixed SPMS decrement and a decrement specific to each EDSS state) to the reference case utility (i.e. 0.870 for patients with RRMS in EDSS 0):

$$HSU\ value = Base\ RRMS\ utility - Disutility\ specific\ to\ each\ EDSS\ state - \ SPMS\ correction$$

Disutilities to the reference case utility were applied for higher EDSS states (for example, a disutility of −0.352 for EDSS 5 was applied to the reference case) and for SPMS subtype (a disutility of −0.045 was applied to the reference case). The methods used to derive HSUs from the study by Orme et al. are presented in Appendix M.

Table 64: Health state utilities derived from other sources considered in the model

EDSS	Orme et al. (Scenario)
0	0.825
1	0.754
2	0.660
3	0.529
4	0.565
5	0.473
6	0.413
7	0.252
8	−0.094
9	−0.240

Abbreviations: EDSS: Expanded Disability Status Scale.

Relapse disutility

An acute relapse event imposes a significant burden in terms of costs and disutility to patients with MS. The model incorporates relapse disutility in the base case analysis.

Relapse disutility from EXPAND was considered as the base case, as the other two sources considered, Orme et al. and Ruutiainen et al., assessed relapse disutility in patients with RRMS.[17, 116] Ruutiainen et al. did not include a patient sample from the UK, however the UK value set was used to estimate HSU values, in line with the NICE reference standard.

Relapse disutility data from EXPAND were derived by fitting a regression to estimate utility considering all confounding factors that affect health-related quality of life in patients with SPMS. The detailed method used for regression analysis is presented in Appendix M. Disutilities according to relapse severity (relapse requiring hospitalisation or not) were not derived due to the low number of relapses reported in the trial. However, the mean duration of relapse according to relapse severity was assessed from EXPAND. Relapse disutility and duration of relapse events derived from EXPAND are shown in Table 65.

Table 65: Sources of relapse disutility considered in the model

Severity	EXPAND (Base case)	Orme et al. 2007*	Ruutiainen et al. 2016*
Relapse not requiring hospitalisation			
Duration (in days)	[redacted]	46	46
Disutility	[redacted]	−0.071	−0.066
Relapse requiring hospitalisation			
Duration (in days)	[redacted]	46	46
Disutility	[redacted]	−0.071	−0.066

*No disutility data available according to relapse severity; Relapse duration considered from original ScHARR model for the appraisal of beta interferons and glatiramer acetate [TA527][52] (referred from Ocrelizumab RRMS NICE submission [TA533][55]).
Abbreviations: RRMS: relapsing-remitting multiple sclerosis; ScHARR: School of Health and Related Research;

The studies by Orme et al. and Ruutiainen et al. do not report relapse disutility according to relapse severity; therefore, the same disutility values were applied to hospitalised and non-hospitalised events on the basis that neither of the sources reported data by hospital status (Table 65).[17, 116] The study by Ruutiainen et al. assessed the relapse disutility from a cross-sectional survey of 553 patients with MS registered with the Finnish Neuro Society, Finland. Relapse disutility was derived by comparing patients with RRMS and EDSS <6 who had experienced at least one relapse in the past year to those patients without relapse. In the regression model controlling for EDSS scores, a statistically significant difference in EQ-5D utility values was observed between patients with MS with and without relapses (difference = 0.066; p=0.012). Limitations in using disutility due to relapse values from the study by Ruutiainen et al. are that (1) the disutility values were derived from a study in Finland, and (2) it is a retrospective study, and, therefore, recollection bias is possible.

Caregiver disutility

MS imposes a significant burden on caregivers.[116] The model incorporates the disutility of caregivers in the base case analysis in line with the previous RRMS submissions to NICE.[100] None of the published studies reported the disutility of caregivers who managed patients with SPMS. Caregivers of patients with SPMS are expected to have more disutility than caregivers of patients with RRMS due to the progressive nature of the disease. A conservative approach was considered in the model by assuming caregiver disutility to be the same for managing SPMS and patients with RRMS.

Disutilities from TA127 and the study by Acaster et al. (identified by the SLR described in Section B.3.4.3) are presented in Table 66.[100, 117] Caregiver disutility from TA127 was considered for the base case analysis as it is widely used and consistently accepted in previous NICE MS appraisals. Caregiver disutility reported in the study by Acaster et al. (used in the cladribine manufacturer submission to NICE) was explored in the scenario analysis.[57]

In the natalizumab NICE submission (TA127), caregiver disutilities were estimated based on EDSS-wise time spent by caregivers obtained from the UK MS survey, 2005 and caregiver disutility from the Alzheimer's disease NICE MTA (TA217).[118] Acaster et al. reported caregiver disutilities from a cross-sectional, observational online survey study of the EQ-5D scores of 200 caregivers and 200 matched controls (e.g. non-caregivers).[117]

Table 66: Sources of caregiver disutilities considered in the model

EDSS	Natalizumab NICE submission (Base case)	Acaster et al. 2013
0	0.000	0.000
1	0.001	0.002
2	0.003	0.045
3	0.009	0.045
4	0.009	0.142
5	0.020	0.160
6	0.027	0.173

7	0.053	0.030
8	0.107	0.095
9	0.140	0.095*
10	0	0

* In the scenario, EDSS 9 was assumed to have the same disutility associated with EDSS 8, as it was not reported by Acaster et al. 2013.
Abbreviations: EDSS: Expanded Disability Status Scale.

B.3.4.2 Mapping

No mapping was performed in this analysis, as EQ-5D data were sourced directly from the EXPAND trial.

B.3.4.3 Health-related quality of life studies

An SLR and update was conducted to identify HRQoL data and preference-based health state utility data for adults with MS and their caregivers. The original utility SLR identified 71 studies from 72 publications, of which 57 publications reported data on HSU values for people with MS in the UK, or using UK tariffs. All 57 used generic preference-based measures of health valuation (EQ-5D). The updated utility SLR identified one additional publication.

Appendix H details the methods and results of the SLR conducted to identify utility studies relevant to treatment options for the management of SPMS. As utility data were available from the EXPAND trial, these have been used in the base case, supplemented as necessary by literature sources, and tested in scenarios, in line with previous NICE appraisals.

B.3.4.4 Adverse reactions

The disutility associated with specific AEs along with the sources are presented in Appendix M. Based on the average proportion of SAEs in the EXPAND study, it was assumed that for each type of AE, [redacted] of the events were non-serious and [redacted] were serious.[55] As an alternative approach, data for AE disutility for each treatment were obtained from the respective NICE technology appraisals (TAs).

The average annual adverse event disutilities used in the model are summarised in Table 67.

Table 67: Average annual adverse event disutilities by DMTs used in the model

DMT	Year 1	Year 2	Year 2+
Siponimod	[redacted]	[redacted]	[redacted]
Dimethyl fumarate	[redacted]	[redacted]	[redacted]
Fingolimod	[redacted]	[redacted]	[redacted]
Glatiramer acetate	[redacted]	[redacted]	[redacted]
Interferon β-1a (Avonex®)	[redacted]	[redacted]	[redacted]
Interferon β-1a (Rebif® 22 µg)	[redacted]	[redacted]	[redacted]
Interferon β-1a (Rebif® 44 µg)	[redacted]	[redacted]	[redacted]
Interferon β-1b (Extavia®)	[redacted]	[redacted]	[redacted]

Natalizumab	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]
Teriflunomide	[redacted]	[redacted]	[redacted]
BSC	0.0000	0.0000	0.0000

Abbreviations: BSC: best supportive care; DMT: disease-modifying therapy.

B.3.4.5 Health-related quality of life data used in the cost-effectiveness analysis

A summary of the utility values used in the cost-effectiveness analysis is provided in Table 68.

Table 68: Summary of utility values for cost-effectiveness analysis

State	Utility value: mean	Reference in submission (section and page number)	Justification
EDSS 0	0.825	Section B.3.4.1, page 108	Orme et al.
EDSS 1	0.754		
EDSS 2	0.660		
EDSS 3	[redacted]		EXPAND trial
EDSS 4	[redacted]		
EDSS 5	[redacted]		
EDSS 6	[redacted]		
EDSS 7	[redacted]		
EDSS 8	−0.094		Orme et al.
EDSS 9	−0.240		
EDSS 10	0		

Abbreviations: EDSS: Expanded Disability Status Scale.

B.3.5 *Cost and healthcare resource use identification, measurement and valuation*

An SLR was conducted to identify relevant cost and healthcare resource use studies in MS. Full details pertaining to the methods and results of the SLR can be found in Appendix I. Twenty-one studies from 26 publications were identified for inclusion, of which ten reported cost and resource use data for UK patients with MS. An update to the economic SLR identified one additional publication. The base case approach was to align closely to the committee preferences expressed in recent NICE appraisals in MS.

The following resource use categories were captured in the analysis: drug acquisition, administration and monitoring costs; disease management and relapse costs; and adverse event management costs.

As per Section B.3.2.2, the perspective is that of the NHS and PSS.

B.3.5.1 Intervention and comparators' costs and resource use

Drug acquisition costs

A summary of the annual drug acquisition costs for DMTs is presented in Table 69. A detailed description on inputs used to calculate annual drug acquisition costs is presented in Appendix M.

The costs of drug acquisition were assumed to apply for the duration that patients remained on therapy. The list prices of DMTs were obtained from the online database of the Monthly Index of Medical Specialties (eMIMS), or the British National Formulary (BNF).

Table 69: Annual drug acquisition, administration and monitoring, and adverse event management costs used in the cost-effectiveness model

DMT	Drug acquisition costs		Drug administration and monitoring costs		Adverse event management costs	
	Year 1	Year 2+	Year 1	Year 2+	Year 1	Year 2+
Siponimod	[redacted]	[redacted]	£733	£307	£22.19	£22.19
PAS Price	[redacted]	[redacted]				
DMF	£17,910	£17,910	£641	£230	£47.56	£47.56
Fingolimod	£19,176	£19,176	£1,157	£288	£62.35	£62.35
PAS Price	£[redacted]	£[redacted]				
GA	£6,704	£6,704	£527	£283	£63.96	£63.96
Interferon β-1a (Avonex®)	£8,531	£8,531	£546	£292	£87.60	£87.60
Interferon β-1a (Rebif® 22 µg)	£8,003	£8,003	£548	£292	£85.60	£85.60
Interferon β-1a (Rebif® 44 µg)	£10,608	£10,608	£548	£292	£85.60	£85.60
Interferon β-1a (Extavia®)	£7,264	£7,264	£546	£292	£102.90	£102.90
PAS Price	£[redacted]	£[redacted]				
Natalizumab	£14,740	£14,740	£7,575	£7,787	£387.64	£387.64
Ocrelizumab	£19,160	£19,160	£2,288	£1,742	£143.12	£143.12
Teriflunomide	£13,538	£13,538	£378	£228	£6.72	£6.72
BSC	£0	£0	£0	£0	£0.00	£0.00

Abbreviations: BSC: best supportive care; DMF: dimethyl fumarate; DMT: disease-modifying therapy; GA: glatiramer acetate; PAS: Patient Access Scheme.

Drug administration and monitoring costs

Annual drug administration and monitoring costs for the included DMTs are shown in Table 69. A detailed description on inputs used to calculate annual drug administration and monitoring costs is presented in Appendix M.

The costs of drug administration and monitoring were assumed to apply for the duration that patients remained on therapy. The annual cost of drug administration and monitoring was calculated from the unit cost of each administration and monitoring resource multiplied by the percentage of patients utilising the resource and number of resources consumed in a year of

treatment. Drug administration and monitoring resources were considered from the recent NICE manufacturer submission and summary of product characteristics of each included DMT. Unit costs for drug administration and monitoring resources were estimated using the NHS reference costs (2017-2018).[119] Costs were inflated to 2018 costs by using the Personal Social Services Research Unit (PSSRU) 2018 values where required.[120] The proportion of patients with SPMS requiring the particular monitoring resource was assumed to be the same as that for the RRMS population for each approved treatment.

All patients require a genotype test before initiation of siponimod treatment to assess CYP2C9 status. Genotyping identifies patients with SPMS with CYP2C9*1*3, CYP2C9*2*3 and CYP2C9*3*3 genotype. Siponimod should not be used in patients with a CYP2C9*3*3 genotype, due an inability to metabolise siponimod. In patients with a CYP2C9*2*3 or *1*3 genotype, the recommended maintenance dose is 1 mg once daily (four tablets of 0.25 mg; 1 mg tablets will be available in [redacted]), due to their reduced ability to metabolise siponimod. Apart from drug administration and monitoring costs, siponimod will incur an additional cost of genotype testing; a cost of £35 has been implemented in the base case to account for this. In practice, it is anticipated that Novartis will bear this cost, but it has been conservatively added to the cost-effectiveness model. Administration and monitoring costs will be the same for patients receiving siponimod doses of 1 mg and 2 mg.

B.3.5.2 Health state unit costs and resource use

Disease management costs

The model takes an NHS/PSS perspective, and only direct costs are considered. For patients with SPMS, the disease management costs were assumed to be the same as those for RRMS, as it is assumed that MS phenotype has no EDSS-independent effect on disease cost. EDSS-wise health state costs from the UK MS survey were reanalysed in the NICE appraisal TA320 and inflated in TA527 to 2014/15 prices. These data were further inflated to 2017/18 prices and are presented in Table 70. The UK MS survey represents the largest dataset (responses from 2,048 people), which estimated NHS and PSS costs and costs funded by the UK government.[117] The NICE appraisal committee for TA527 considered that the NHS and PSS costs estimated from the UK MS survey were the best available data; given the recent rejection of other possible cost sources no scenarios have been presented for these inputs.[52]

Table 70: EDSS-wise disease management costs in the model

EDSS	UK MS Survey[52] as reanalysed in TA320 and then inflated to 2017/18
0	£965
1	£1,004
2	£736
3	£4,024
4	£1,949
5	£3,307
6	£4,415
7	£11,621
8	£28,304
9	£22,648
10	£0

Abbreviations: EDSS: Expanded Disability Status Scale; MS: multiple sclerosis.

Relapse costs

Relapse management costs are applied according to the severity of relapse (requiring and not requiring hospitalisation). Relapse management costs for patients with SPMS were assumed to be the same as those for patients with RRMS. Three different sources were considered for relapse management costs, as shown in Table 71. Relapse management costs from TA527 were considered as the base case model inputs;[52] data from other sources, as identified by the cost and resource use SLR (Section B.3.5), were explored in the scenario analysis.

Table 71: Relapse management costs used in the model

Source	Relapse not requiring hospitalisation	Relapse requiring hospitalisation
TA527 - RSS model & ScHARR analysis[52] (Base case)	£4,357	£4,357
Hawton et al. 2016[22]	£407	£3,825
Tyas et al. 2007[121]	£1,962	£1,962

Abbreviations: RSS: risk sharing scheme; ScHARR: School of Health and Related Research.

B.3.5.3 Adverse reaction unit costs and resource use

Annual AE management costs for each DMT were shown in Table 69. A detailed description on inputs used to calculate annual AE management costs is presented in Appendix M.

AEs and their associated costs were estimated based on the resources used to manage each AE. The resource use to manage each AE was obtained from recent RRMS HTA manufacturer submissions to NICE.

B.3.6 *Summary of base-case analysis inputs and assumptions*

B.3.6.1 Summary of base-case analysis inputs

The base case model inputs and settings are presented in Table 72.

Table 72: Summary of variables applied in the economic model

Variable	Value	Measurement of uncertainty and distribution	Reference to section in submission
Model Properties			
Perspective	NHS/PSS	None	B.3.2.2
Time horizon	Lifetime (dependent on cohort age: 53 cycles in base case)	Varies with age	B.3.2.2
Cycle length	1 year	None	B.3.2.2
Cohort size	1,000	None	B.3.3.1
Population	ITT	None	B.3.3.1

Age (Mean age of cohort)	48 years	Gamma	B.3.3.1
% male patients	39.9%	Beta	B.3.3.1
Baseline EDSS distribution	EXPAND	Dirichlet distribution	B.3.3.1
Upper limit of EDSS to still receive DMT	6.5	None	B.3.2.3
Discount rates for costs and benefits	3.5%	None	B.3.2.2
Source of NH disability progression	EXPAND + London Ontario	Dirichlet distribution	B.3.3.2
Source of NH ARR approach / source	Relapse as a function of EDSS – Patzold 1982 and UK MS survey	Log-normal distribution	B.3.3.3
Source of general population mortality	ONS, UK	None	NA
Mortality multiplier	EDSS-dependent mortality multiplier – Pokorski 1997	Log-normal distribution	B.3.3.4
Primary endpoint	6-month CDP	None	B.3.3.2
Source of effectiveness – disability progression	MAIC	Log-normal distribution	B.3.3.2
Source of effectiveness – relapse	MAIC	Log-normal distribution	B.3.3.3
Source of adverse events incidence	EXPAND + TA533	Beta distribution	B.3.3.6
Discontinuation approach chosen	Time-dependent discontinuation rates	None	B.3.3.5
Source of discontinuation data	ITC of EXPAND and comparator SPMS trials	Beta distribution	B.3.3.5
Utilities			
Health state utilities	EXPAND + Orme	Beta distribution	B.3.4.1
Relapse disutility	EXPAND	Beta distribution	B.3.4.1
Caregiver disutility	Natalizumab for RRMS NICE submission (TA127)	Beta distribution	B.3.4.1
Costs			
Drug acquisition costs	Dosing schedule taken from summary of product characteristics of individual DMTs List price taken from eMIMS	None	B.3.5.1
Drug administration and monitoring costs	Resource use was based on summary of product characteristics of each drug and	Log-normal distribution	B.3.5.1

	recent HTA submissions Unit costs of resources were taken from NHS reference costs and PSSRU 2017/18		
Adverse event monitoring costs	Adverse event management resources considered from recent HTA submissions Unit costs of resources were taken from NHS reference costs and PSSRU 2017/18	Log-normal distribution	0
Health state costs	UK MS Survey costs	Log-normal distribution	B.3.5.2
Relapse costs	TA527 – RSS model & ScHARR analysis	Log-normal distribution	B.3.5.2
Cost of genotyping for siponimod	£35	Log-normal distribution	B.3.5.1

Abbreviations: ARR: annualised relapse rate; CDP: confirmed disability progression; DMT: disease modifying therapy; EDSS: Expanded Disability Status Scale; eMIMS: electronic Monthly Index of Medical Specialities; HTA: Health Technology Assessment; ITC: indirect treatment comparison; ITT: intention-to-treat; MAIC: matching adjusted indirect comparison; MS: multiple sclerosis; NH: natural history; NHS: National Health Service; ONS: Office for National Statistics; PSS: Personal Social Services; PSSRU: Personal Social Services Research Unit; RRMS: relapsing-remitting multiple sclerosis; RSS: risk sharing scheme; ScHARR: School of Health and Related Research; SPMS: secondary progressive multiple sclerosis.

B.3.6.2 Assumptions

The following assumptions were considered for the cost-effectiveness model:

- The patient population in EXPAND and the Active SPMS subgroup are representative of the NHS population eligible for treatment with siponimod
- **Treatment does not have any impact on severity or duration of relapses:** No impact of the effectiveness of DMTs on relapse severity and duration was considered for the following reasons:
    - Scarce evidence on the effect of DMTs on relapse duration and severity
    - Impact of relapse severity and duration on incremental cost-effectiveness ratios (ICERs) is negligible as relapses occur less frequently in patients with SPMS (due to the progressive course of the disease) than in patients with RRMS
- **Patients with SPMS may progress or regress in EDSS states and treatment effect is applied to EDSS progression but not regression:** Patients with SPMS and EDSS <5.0 receiving placebo in EXPAND were found to regress (move to lower EDSS states). To account for this, the model allows regression in patients with SPMS. However, as a conservative assumption, the treatment effect of DMTs is applied only to EDSS progression but not to EDSS regression, in line with all previous NICE appraisals

- **Patients discontinue treatment once they reach EDSS score 7.0:** In line with ABN guidelines, patients with SPMS who reach EDSS 7.0 discontinue treatment, as the EXPAND trial does not provide any evidence to determine efficacy in patients with EDSS ≥7.0
- **Treatment benefits are accrued only during the treatment period:** It is assumed that treatment effects of DMTs are accrued only during DMT treatment; after discontinuing the DMT, patients will move to BSC and no residual treatment effect is modelled in patients
- **Treatment has no direct survival benefit:** It is assumed that DMTs will not have any impact on mortality rate directly. However, patients receiving siponimod might survive for a longer period vs patients receiving BSC as siponimod slows disability progression (patients in lower EDSS states have lower mortality risk compared with patients in higher EDSS states)
- **Relapses have no residual effect on EDSS:** Impact of relapses are included as costs and disutility according to relapse severity. It is assumed that relapse will not have any impact on EDSS progression or regression
- **Constant rate of AEs:** AEs are assumed to occur at a constant rate in patients receiving DMTs and are assumed to stop after discontinuing DMTs. A similar approach was used in previous NICE RRMS submissions[55, 56]

B.3.7 *Base-case results*

Base-case results for the cost-effectiveness analysis are presented in the following subsections.

B.3.7.1 Base-case incremental cost-effectiveness analysis results

The base case cost-effectiveness results are presented in Table 73, using the with-PAS price for siponimod and the with-PAS price for Extavia®. Siponimod was associated with a pairwise ICER of £[redacted] per QALY gained vs Extavia®.

Table 73: Base-case results (MAIC – 6-month CDP)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Extavia®	£[redacted]	15.86	3.17	-	-	-	-
Siponimod	£[redacted]	16.16	4.49	£[redacted]	0.30	1.32	£[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life-years gained; QALYs: quality-adjusted life-years.

B.3.8 *Sensitivity analyses*

B.3.8.1 Probabilistic sensitivity analysis

Probabilistic sensitivity analyses (PSA) were generated by assigning distributions to all input parameters and randomly sampling from these distributions over 1,000 Monte Carlo simulations, in order to calculate the uncertainty in costs and outcomes; 1,000 simulations was deemed appropriate based on the results of an ICER convergence test, shown in Figure 16, which show the ICER converging towards its probabilistic value.

Results of the PSA for the comparison of siponimod (at PAS price) versus Extavia® (at PAS price) are summarised in Table 74. The probabilistic results taking into account the combined uncertainty across model parameters are very similar to the deterministic base case analysis (ICER differs by less than £[redacted].

Table 74: Base case results (probabilistic)

Treatment	Costs	LYs	QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Extavia®	£[redacted]	NR	3.12	-	-	-	
Siponimod	£[redacted]	NR	4.41	£[redacted]	NR	1.25	£[redacted]

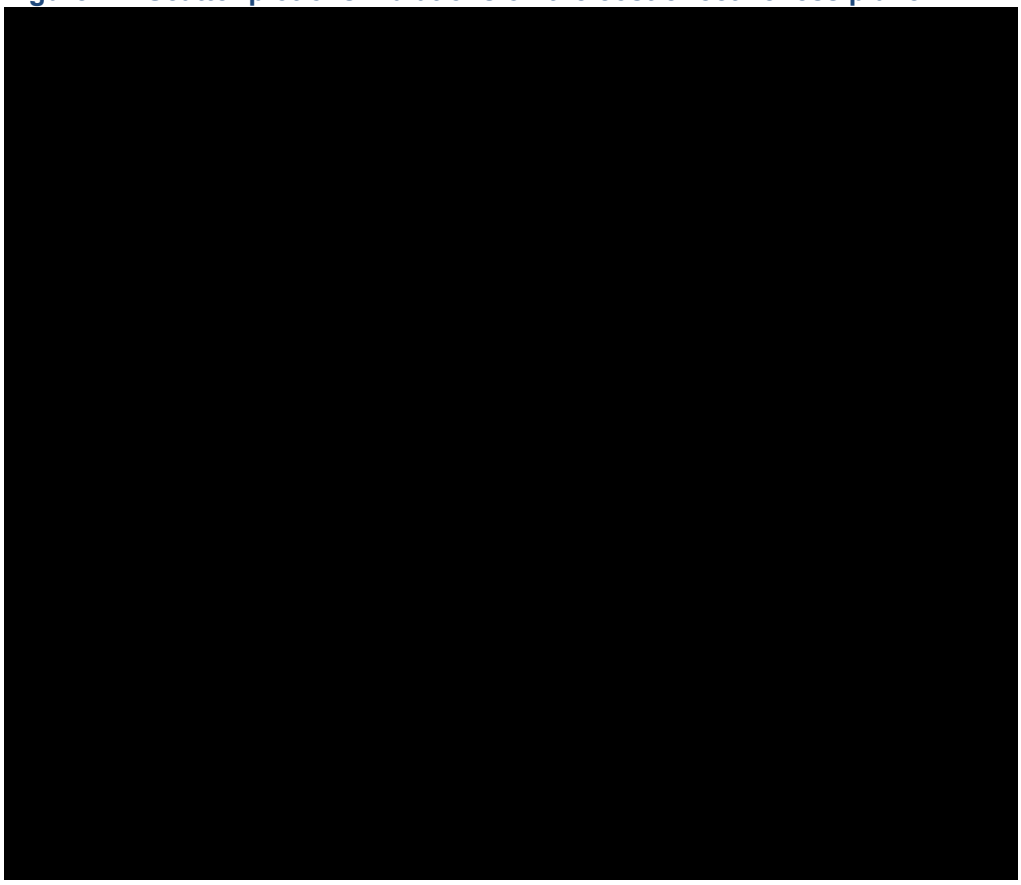
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life-years gained; NR: not reported (by the model); QALY, quality-adjusted life-year.

Figure 16: Probabilistic ICER convergence plot

Abbreviations: ICER: incremental cost-effectiveness ratio.

A scatter plot of the joint distribution of incremental costs and incremental QALYs from the PSA is shown in Figure 17, and the cost-effectiveness acceptability curves corresponding with the above outputs is presented in Figure 18.

Figure 17: Scatter plot of simulations on the cost-effectiveness plane



Abbreviations: WTP: willingness to pay; QALY: quality-adjusted life-year.

Figure 18: Cost-effectiveness acceptability curves

The probabilities of siponimod being the most cost-effective treatment option at willingness to pay thresholds of £20,000 and £30,000 per QALY are presented in Table 75.

Table 75: Probability of cost-effectiveness

Comparator	Probability of cost-effectiveness at a £20,000 per QALY threshold	Probability of cost-effectiveness at a £30,000 per QALY threshold
Extavia®	[redacted]	[redacted]
Siponimod	[redacted]	[redacted]

Abbreviations: QALY: quality-adjusted life-year.

B.3.8.2 Deterministic sensitivity analysis

A one-way deterministic sensitivity analysis was undertaken and reported in Figure 19. Where possible, upper and lower bounds were based on confidence intervals reported in the literature. In all other cases, bounds were assumed to be ±20% of the parameter value, in the absence of data. The tornado plot shows the top ten drivers of cost-effectiveness in the comparison of siponimod and Extavia; within the plot, it can be seen that the most influential parameters were the estimates of effectiveness on disability progression for each DMT. Other than disability progression, results were largely robust to parameter uncertainty with age (which implicitly adjusts the model time horizon to maintain a lifetime time horizon), being the only other parameter that crossed the cost-effectiveness threshold at one bound. This demonstrates the stability of the model results to parameter uncertainty, other than relative effectiveness.

Figure 19: Deterministic sensitivity analysis results (ICERs)

Abbreviations: CDP: confirmed disability progression; EDSS: Expanded Disability Status Scale; HSU: health-state utilities; ICER: incremental cost-effectiveness ratio; ITT: intention-to-treat; MS: multiple sclerosis; NHS: National Health Service; PSS: Personal Social Services; QALY: quality-adjusted life-year.

B.3.8.3 Scenario analysis

Scenario analyses on model input and assumption choices

Extensive deterministic scenario analyses were conducted to evaluate the robustness of the ICER estimates. The scenario analyses involved replacing a parameter (or group of parameters) with another plausible value(s) in order to examine the impact of a new “scenario”; all other inputs and settings remained aligned with the base case. This provided a single ICER estimate associated with the new scenario. The scenario analyses presented are:

- Alternative source of natural history disability progression
- Alternative source of natural history of relapses
- Alternative treatment discontinuation
- Alternative source of adverse events
- Alternative health state utility values
- Alternative source of relapse disutility
- Alternative source of caregiver disutility
- Alternative source of relapses costs

The results of the deterministic scenario analyses are presented in Table 76.

Table 76: Scenario analysis results

Scenario	Treatment	Costs	QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Alternative source of natural history disability progression **Base case:** Combining EXPAND placebo-arm data with London Ontario data **Scenario:** London Ontario database	**Extavia®**	[redacted]	2.08	-	-	-
	Siponimod	[redacted]	3.20	[redacted]	1.12	[redacted]
Alternative source of natural history disability progression **Base case:** Combining EXPAND placebo-arm data with London Ontario data **Scenario:** British Columbia	**Extavia®**	[redacted]	5.64	-	-	-
	Siponimod	[redacted]	6.73	[redacted]	1.08	[redacted]
Alternative source of natural history of relapses **Base case:** Combining EXPAND data with Patzold et al. 1982 plus UK MS survey **Scenario:** Patzold et al. 1982 plus UK MS survey	**Extavia®**	[redacted]	3.15	-	-	-
	Siponimod	[redacted]	4.47	[redacted]	1.32	[redacted]
Alternative treatment discontinuation **Base case:** Time-dependent **Scenario:** Time-independent	**Extavia®**	[redacted]	3.18	-	-	-
	Siponimod	[redacted]	4.88	[redacted]	1.70	[redacted]
Alternative source of adverse events	**Extavia®**	[redacted]	3.22	-	-	-

Scenario	Treatment	Costs	QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Base case: EXPAND data supplemented with TA533 **Scenario:** EXPAND with individual comparator TAs	**Siponimod**	[redacted]	4.49	[redacted]	1.27	[redacted]
Alternative health state utility values **Base case:** EXPAND data plus Orme et al. 2007 **Scenario:** Orme et al. 2007 only	**Extavia®**	[redacted]	2.08	-	-	-
	Siponimod	[redacted]	3.25	[redacted]	1.17	[redacted]
Alternative source of relapse disutility **Base case:** EXPAND data **Scenario:** Orme et al. 2007	**Extavia®**	[redacted]	3.17	-	-	-
	Siponimod	[redacted]	4.50	[redacted]	1.32	[redacted]
Alternative source of relapse disutility **Base case:** EXPAND data **Scenario:** Ruutiainen et al. 2016	**Extavia®**	[redacted]	3.17	-	-	-
	Siponimod	[redacted]	4.50	[redacted]	1.32	[redacted]
Alternative source of caregiver disutility **Base case:** TA127 **Scenario:** Acaster et al. 2013	**Extavia®**	[redacted]	2.25	-	-	-
	Siponimod	[redacted]	3.37	[redacted]	1.12	[redacted]
Alternative source of relapse costs **Base case:** Tyas et al. 2007 **Scenario:** TA527 RSS	**Extavia®**	[redacted]	3.17	-	-	-
	Siponimod	[redacted]	4.49	[redacted]	1.32	[redacted]

Scenario	Treatment	Costs	QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Alternative source of relapse costs **Base case:** Tyas et al. 2007 **Scenario:** Hawton et al. 2007	**Extavia®**	[redacted]	3.17	-	-	-
	Siponimod	[redacted]	4.49	[redacted]	1.32	[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; LY: life-year; LYG: life-years gained; MS: multiple sclerosis; QALY: quality-adjusted life-year; RSS: risk sharing scheme; TA: technology appraisal.

Scenario analyses considering alternative comparators

As described in Section B.1.3, RRMS and SPMS inherently overlap and many RRMS DMTs will continue to be used throughout the transition to SPMS and would be displaced were siponimod to be recommended by NICE. To explore the cost-effectiveness of siponimod vs other comparators, scenario analyses were conducted making the following assumptions:

- Avonex, Rebif 44 and Rebif 22:
    - TA527 concluded that interferons were equal in efficacy and that Extavia was the least costly; TA527 applied one set of efficacy inputs to all interferons and glatiramer acetate and the approach taken is aligned to that
    - Therefore, in the absence of 6-month CDP data for these comparators, the base case ICER vs Extavia using 6-month CDP is, by definition, higher than any ICER vs other more costly interferons (Extavia reported the lowest ICER in TA527 when considering the same efficacy for all treatments); consequently, no new ICERs are presented for these scenarios
- Glatiramer acetate:
    - TA527 concluded that interferons were equal in efficacy and applied one set of efficacy inputs to all interferons and glatiramer acetate and the approach taken is aligned to that
    - As the cost of glatiramer acetate is not known to be greater than that for Extavia (in contrast to the other interferons noted above), an analysis was undertaken where the price of Extavia was replaced by the list price of glatiramer acetate (Brabio)
- Natalizumab uses the proportion of patients with 6-month CDP at week 96 MAIC OR and ARR from the ASCEND trial
- All other comparators:

- Comparators use 6-month CDP HR and ARR equal to 1 – this is a reasonable assumption for CDP, given the lack of RCT evidence and that even DMTs with high efficacy in RRMS have failed to demonstrate efficacy on CDP in SPMS, but is biased against the comparator for ARR where ongoing efficacy is likely; however, it is known that relapse efficacy has very little influence on the ICER
- Siponimod uses EXPAND ITT 6-month CDP HR and ARR

The results of these scenarios are presented in Table 76 and show that siponimod is cost-effective in all scenarios, however the interpretability of these results is limited by the presence of a number of confidential PAS for comparator DMTs.

Table 77: Scenario analysis results on choice of comparator

Scenario	Treatment	Costs	LYs	QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Avonex **Rebif 44** **Rebif 22**	See base case vs Extavia as a conservative proxy for this analysis							
Glatiramer acetate (at list price; a confidential PAS is available)	**Glatiramer acetate**	£273,117	15.86	3.17	-	-	-	-
	Siponimod	[redacted]	16.16	4.49	[redacted]	0.30	1.32	[redacted]
Natalizumab	**Natalizumab**	£347,414	15.78	2.79	-	-	-	-
	Siponimod	[redacted]	15.93	3.54	[redacted]	0.15	0.75	[redacted]
Dimethyl fumarate (at list price; a confidential PAS is available)	**Dimethyl fumarate**	£317,805	15.81	2.99	-	-	-	-
	Siponimod	[redacted]	15.97	3.71	[redacted]	0.16	0.72	[redacted]

Scenario	Treatment	Costs	LYs	QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Fingolimod (at PAS price)	**Fingolimod**	[redacted]	15.81	2.98	-	-	-	-
	Siponimod	[redacted]	15.97	3.71	[redacted]	0.16	0.73	[redacted]
Ocrelizumab (at list price; a confidential PAS is available)	**Ocrelizumab**	£328,853	15.81	2.95	-	-	-	-
	Siponimod	[redacted]	15.97	3.71	[redacted]	0.16	0.76	[redacted]
Teriflunomide (at list price; a confidential PAS is available)	**Teriflunomide**	£300,734	15.81	3.01	-	-	-	-
	Siponimod	[redacted]	15.97	3.71	[redacted]	0.16	0.71	[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; LY: life-year; LYG: life-years gained; PAS: Patient Access Scheme; QALY: quality-adjusted life-year.

B.3.8.4 Summary of sensitivity analyses results

Relative effectiveness on disability progression is the key uncertainty in the decision problem

While the base case average probabilistic ICER is closely aligned with the base case deterministic ICER, the tornado diagrams, probabilistic scatter plot and probability of being cost-effective all reflect the uncertainty surrounding the disability progression parameter estimates. Nonetheless, at the £30,000/QALY willingness to pay threshold typically applied by NICE to MS appraisals, siponimod was found to have a [redacted] probability of being the cost-effective option in the base case, which suggests that the level of uncertainty is acceptable at the proposed PAS price.

Residual parameter uncertainty and modelling assumptions have limited effect on cost-effectiveness

The one-way sensitivity analyses revealed the model to be otherwise largely robust to parameter uncertainty with most remaining parameters (other than relative effectiveness on disability progression) being input choices repeatedly favoured by NICE such as EDSS health state costs and utility values. The further scenario analyses found the model results to be robust to most alternative input choices save for the use of a mixed RRMS–SPMS transition matrix for the natural history; use of this alternative matrix is clearly unrealistic in SPMS given the nature of the condition.

B.3.9 *Subgroup analysis*

Given the infeasibility of a MAIC in the Active subgroup due to the lack of data for comparator trials (see Section B.2.9.3), the subgroup analysis for Active SPMS continued to use the available MAIC data in line with the base case. In effect these analyses differ from the base case only in the baseline characteristics used, which are taken from the EXPAND trial Active SPMS subgroup. The Active SPMS scenario is presented for Extavia (Table 78) and in line with the base case, this ICER can also be considered a conservative estimate versus other interferons. The subgroup scenario found the ICER to be more favourable than the base case.

Table 78: Active SPMS subgroup analysis

Treatment	Costs	LYs	QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Extavia®	[redacted]	16.23	3.11	-	-	-	-
Siponimod	[redacted]	16.52	4.46	[redacted]	0.29	1.35	[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; LY: life-year; LYG: life-years gained; QALY: quality-adjusted life-year.

B.3.10 *Validation*

B.3.10.1 Model structure, input and assumption validation

As described throughput Section B.3, throughout model design and input selection close attention was paid to the many NICE appraisal in MS undertaken between 1999 – 2019 in both RRMS and PPMS. The overall model structure has also been validated through iterative discussions with UK clinical and health economics experts during development. Additionally, further UK clinical input was sought during a teleconference with one clinical expert in April 2019 and at an Advisory Board with five clinical experts in June 2019.

The model structure chosen, a cohort Markov model following progression by EDSS, with relapses modelled as events is aligned to previous NICE models. Model input parameters were derived from the EXPAND study where possible to reflect the decision problem for the present appraisal, but otherwise were very largely based on those preferred as parameter sources in previous appraisals. Parameters derived from EXPAND were typically tested against prior appraisal parameters, where available, to ensure that the model was robust to parameter uncertainty. Similarly, where modelling assumptions were required, previous appraisals were taken as a guide and in cases where previous assumptions were considered inapplicable, this has been justified.

B.3.10.2 Model cross validation

It not possible to cross validate the model outputs as no previous UK models focused on SPMS alone. As noted above, the structure and inputs are very largely consonant with prior NICE appraisals and one-way sensitivity analyses show similar parameters being most influential on the ICER as prior NICE appraisals in RRMS have found. Total QALYs reported in the present model are lower than those reported in previous RRMS appraisals, as would be expected in an older cohort with more advanced disease.

B.3.10.3 Model internal technical validation and quality assurance

An in-depth technical quality-control check of the model was conducted, checking all formulae, calculations and programming, in order to verify the model with regard to technical implementation, model structure and content. A ‘stress-test’ of the model was also performed to validate model semantics and ensure that it responds as anticipated, without producing logically counterintuitive results. The results of the performed stress tests are found in Table 79. The validation process also aimed to ensure that a high degree of transparency was maintained throughout the model and so adaptations were carried out where necessary to ensure the validity of the cost-effectiveness model.

Table 79. Cost-effectiveness model validation: sanity check

Test	Expected effect	Observed effect
Set initial number of patients (cohort size) to 0	Intervention and comparator costs and QALYs equal 0	As expected
Set initial number of patients (cohort size) to 1	ICER does not change	As expected

Set both treatment and comparator to same intervention	Costs and QALYs across all treatments are equal	As expected
Set mortality rate to 0% at all ages	Costs increase as there are no deaths in the model	As expected
Set mortality rate to 100% at all ages	Costs fall and no deaths in the model	As expected
Increase/decrease mortality rate	Costs are reduced	As expected
Set the costs of treatments to 0	Drug acquisition costs equal 0	As expected
Double the costs of treatments	Drug acquisition costs double	As expected
Increase/decrease the cost of treatments	Drug acquisition costs increase/decrease	As expected
Separately set administration and monitoring, AE, disease management and relapse costs to 0	Each cost components equal 0	As expected
Separately double administration and monitoring, AE, disease management and relapse costs	Each cost components double	As expected
Separately increase/decrease administration and monitoring, AE, disease management and relapse costs	Each cost components increase/decrease	As expected
Set all costs to 0 simultaneously	All costs equal 0	As expected
Alter time horizon (5, 10, 15, 20 and 50 years)	Total costs and QALYs increase/decrease in accordance with longer/shorter horizons	As expected
Set discount rates to 0%	Undiscounted results equal discounted results	As expected
Set discount rates to 100%	Costs and QALYs reduce significantly	As expected
Run the one-way sensitivity analysis and check all input parameters affect results when values are changed	Any input parameters affect the incremental QALYs, costs or both (unless it has an exactly equal effect on all arms in the model)	As expected
Set the health state utilities the same for all EDSS health states	LY to QALY ratio are the same across all treatments	As expected
Set the utilities for all EDSS health states to 1 and relapse, caregiver and adverse events to 0	QALYs equal Lys for each treatment	As expected
Set all efficacy data equal across treatments, and set disutility associated with adverse events to 0	QALYs and LYs for each treatment are equal	As expected

Abbreviations: AE: adverse event; EDSS: Expanded Disability Status Scale; ICER: incremental cost-effectiveness ratio; LY: life-year; QALY: quality-adjusted life-year.

B.3.11 *Interpretation and conclusions of economic evidence*

Summary of economic evidence for siponimod

When considering the 6-month CDP MAIC base case comparison to Extavia, siponimod is cost-effective based on the deterministic and probabilistic results. Sensitivity and scenario analyses indicate that relative effectiveness on disability progression is the key uncertainty in the model, with no other parameter uncertainty or input choice driving the ICER to a substantial degree.

There is considerable parameter uncertainty in relative effectiveness inputs and further uncertainty with respect to the correct choice of relative effectiveness inputs. Nonetheless the probabilistic results show that siponimod has a [redacted] probability of being the cost-effective option at a willingness-to-pay threshold of £30,000/QALY.

Scenario analyses considering other DMTs with no proven effect on disability progression in SPMS were favourable.

Generalisability of the analysis

As a well-designed and recent RCT, analyses based on the EXPAND trial are expected to be generalisable to the SPMS population in current NHS practice. Use of MAIC analyses to allow comparison with Extavia is selective for a more active subset of the EXPAND trial: average age and baseline EDSS are lowered, the proportion of patients experiencing relapses in the two years prior to the trial is increased, as is the average number of relapses per patients in the two years prior to the trial. Nonetheless, the post-matching and adjustment of baseline characteristics remain representative of the expected position of siponimod in NHS practice, where it will displace continued treatment with DMTs initially started for RRMS.

A number of comparators are subject to confidential PAS arrangements, precluding the presentation of ICERs relevant for decision making within the submission; however, as TA527 indicates that Extavia is the lowest-cost interferon (based on equal efficacy of interferons and also glatiramer acetate), it is clear that the ICER vs Extavia is higher than ICERs vs other interferons and therefore conservative with respect to this appraisal.

Strengths of the economic evaluation

The health economic model has been developed in line with the rich tradition of prior NICE appraisals in RRMS, all of which have conceptualised the disease process in the same way based on EDSS health states with relapses and AEs modelled as additional events. Many of the natural history, utility and cost and resource use inputs have been well established and tested in multiple prior appraisals. Where available these have been supplemented by natural history and utility data from the EXPAND trial; scenario analyses using non-EXPAND sources have not revealed significant uncertainty in the model results arising from the choice of literature or trial-based inputs. Sensitivity and scenario analyses show the model results to be robust to parameter uncertainty other than disability progression.

Limitations of the economic evaluation

Lack of comparator RCT data that can be compared directly with EXPAND in a standard NMA framework result in parameter uncertainty on relative effectiveness on disability progression, the key model driver. EXPAND trial data are only available for EDSS levels in the trial, requiring the admixture of literature sources for natural history and utility to the EXPAND data. To retain comparability with previous appraisals, reflect the availability of natural history and utility data, and evidence for other DMTs, the model structure does not capture the effect of siponimod upon cognition; as a result, all ICERs are likely to be higher than if this effect had been modelled. It is assumed that patients with SPMS may progress or regress in EDSS states and treatment effect is applied to EDSS progression but not regression; if the effect of siponimod was to promote regression as well as delay progression, this assumption will result in the ICER not reflecting the full benefit of siponimod.

Conclusion

In spite of the limited comparator trial data, and the differences in trial design, baseline characteristics and placebo-arm responses, use of the MAIC allowed a cost-effectiveness analysis to be undertaken. Probabilistic analysis found that even when the parameter uncertainty in relative effectiveness was taken into consideration, siponimod had a [redacted] probability of being the most cost-effective option at a willingness-to-pay threshold of £30,000/QALY. Given that Extavia with PAS is [redacted] other DMTs that may be displaced by siponimod.

References

1. National Institute for Clinical Excellence (NICE). Siponimod for treating secondary progressive multiple sclerosis: Final scope. https://www.nice.org.uk/guidance/gid-ta10436/documents/final-scope. Accessed 06-Sep-2019.
2. Novartis Data on File. Draft Summary of Product Characteristics for Siponimod.
3. Kappos L, Bar-Or A, Cree BAC, et al. Siponimod versus placebo in secondary progressive multiple sclerosis (EXPAND): a double-blind, randomised, phase 3 study. Lancet 2018;391:1263-1273.
4. Peterson LK, Fujinami RS. Inflammation, demyelination, neurodegeneration and neuroprotection in the pathogenesis of multiple sclerosis. J Neuroimmunol 2007;184:37-44.
5. Multiple Sclerosis Trust. MS: the facts. https://www.mstrust.org.uk/about-ms/what-ms/ms-facts. Accessed 05-Mar-2019.
6. National Institute for Health and Clinical Excellence (NICE). Fingolimod for the Treatment of Relapsing-Remitting Multiple Sclerosis in Adults. Single technology appraisal (STA). Novartis Pharmaceuticals UK Ltd Company Submission. https://www.nice.org.uk/guidance/ta254/documents/manufacturer-submission-from-novartis2. Accessed 05-Mar-2019.
7. Multiple Sclerosis Trust. Prevalence and incidence of multiple sclerosis. https://www.mstrust.org.uk/a-z/prevalence-and-incidence-multiple-sclerosis. Accessed 05-Mar-2019.
8. Ontaneda D, Fox RJ. Progressive multiple sclerosis. Curr Opin Neurol 2015;28:237-43.
9. Lublin FD, Reingold SC, Cohen JA, et al. Defining the clinical course of multiple sclerosis: the 2013 revisions. Neurology 2014;83:278-86.
10. Larochelle C, Uphaus T, Prat A, et al. Secondary Progression in Multiple Sclerosis: Neuronal Exhaustion or Distinct Pathology? Trends Neurosci 2016;39:325-339.
11. Multiple Sclerosis Trust. Types of MS. https://www.mstrust.org.uk/about-ms/what-ms/types-ms. Accessed 05-Mar-2019.
12. Lublin FD, Reingold SC. Defining the clinical course of multiple sclerosis: results of an international survey. National Multiple Sclerosis Society (USA) Advisory Committee on Clinical Trials of New Agents in Multiple Sclerosis. Neurology 1996;46:907-11.
13. Inojosa H, Proschmann U, Akgun K, et al. A focus on secondary progressive multiple sclerosis (SPMS): challenges in diagnosis and definition. J Neurol 2019.
14. Novartis Data on File (Caseby SCL; Montgomery SM; Woodhouse FA; Kroes MK). [Manuscript under development] Transition to secondary progressive multiple sclerosis: the consequences for patients and healthcare systems, a healthcare professional survey 2019.
15. National Institute for Clinical Excellence (NICE). Multiple sclerosis in adults: management. https://www.nice.org.uk/guidance/cg186/resources/multiple-sclerosis-in-adults-management-pdf-35109816059077. Accessed 31-May-2019. 2014.

16. Scalfari A, Neuhaus A, Daumer M, et al. Onset of secondary progressive phase and long-term evolution of multiple sclerosis. J Neurol Neurosurg Psychiatry 2014;85:67-75.
17. Orme M, Kerrigan J, Tyas D, et al. The effect of disease, functional status, and relapses on the utility of people with multiple sclerosis in the UK. Value Health 2007;10:54-60.
18. Simpson Jr S, Mina S, Morris H, et al. The epidemiology of multiple sclerosis in the Isle of Man: 2006–2011. Acta Neurologica Scandinavica 2015;132:381-388.
19. Katz Sand I, Krieger S, Farrell C, et al. Diagnostic uncertainty during the transition to secondary progressive multiple sclerosis. Mult Scler 2014;20:1654-7.
20. Davies F, Wood F, Brain KE, et al. The Transition to Secondary Progressive Multiple Sclerosis: An Exploratory Qualitative Study of Health Professionals' Experiences. Int J MS Care 2016;18:257-264.
21. Bogosian A, Morgan M, Moss-Morris R. Multiple challenges for people after transitioning to secondary progressive multiple sclerosis: a qualitative study. BMJ Open 2019;9:e026421.
22. Hawton A, Green C. Health Utilities for Multiple Sclerosis. Value Health 2016;19:460-8.
23. Mohr DC, Hart SL, Fonareva I, et al. Treatment of depression for patients with multiple sclerosis in neurology clinics. Mult Scler 2006;12:204-8.
24. Wallin MT, Wilken JA, Turner AP, et al. Depression and multiple sclerosis: Review of a lethal combination. J Rehabil Res Dev 2006;43:45-62.
25. Tauil CB, Grippe TC, Dias RM, et al. Suicidal ideation, anxiety, and depression in patients with multiple sclerosis. Arq Neuropsiquiatr 2018;76:296-301.
26. Brenner P, Burkill S, Jokinen J, et al. Multiple sclerosis and risk of attempted and completed suicide - a cohort study. Eur J Neurol 2016;23:1329-36.
27. Multiple Sclerosis Trust. Secondary Progressive Multiple Sclerosis. https://support.mstrust.org.uk/file/SPMS-A5-Booklet-Oct-2018-FINAL-WEB.pdf. Accessed 05-Mar-2019.
28. MS Society. Social care and the MS community. https://www.mssociety.org.uk/care-and-support/resources-and-publications/publications-search/social-care-and-the-ms-community. Accessed 29-Jul-2019.
29. Thompson A, Kobelt G, Berg J, et al. New insights into the burden and costs of multiple sclerosis in Europe: Results for the United Kingdom. Mult Scler 2017;23:204-216.
30. Bevan S, Zheltoukhova K, McGee R, et al. Ready to Work? Meeting the employment and career aspirations of people with Multiple Sclerosis. The Work Foundation 2011.
31. Pan S, Gray NS, Gao W, et al. Discovery of BAF312 (Siponimod), a Potent and Selective S1P Receptor Modulator. ACS Med Chem Lett 2013;4:333-7.
32. Gajofatto A. Spotlight on siponimod and its potential in the treatment of secondary progressive multiple sclerosis: the evidence to date. Drug Des Devel Ther 2017;11:3153-3157.
33. Gergely P, Nuesslein-Hildesheim B, Guerini D, et al. The selective sphingosine 1-phosphate receptor modulator BAF312 redirects lymphocyte

distribution and has species-specific effects on heart rate. Br J Pharmacol 2012;167:1035-47.
34. Scott FL, Clemons B, Brooks J, et al. Ozanimod (RPC1063) is a potent sphingosine-1-phosphate receptor-1 (S1P1) and receptor-5 (S1P5) agonist with autoimmune disease-modifying activity. Br J Pharmacol 2016;173:1778-92.
35. Akbulak RÖ, Rosenkranz SC, Schaeffer BN, et al. Acute and long-term effects of fingolimod on heart rhythm and heart rate variability in patients with multiple sclerosis. Multiple Sclerosis and Related Disorders 2018;19:44-49.
36. Kappos L, Radue E-W, O'Connor P, et al. A Placebo-Controlled Trial of Oral Fingolimod in Relapsing Multiple Sclerosis. New England Journal of Medicine 2010;362:387-401.
37. Forrest M, Sun S-Y, Hajdu R, et al. Immune Cell Regulation and Cardiovascular Effects of Sphingosine 1-Phosphate Receptor Agonists in Rodents Are Mediated via Distinct Receptor Subtypes. Journal of Pharmacology and Experimental Therapeutics 2004;309:758-768.
38. Chun J, Hartung HP. Mechanism of action of oral fingolimod (FTY720) in multiple sclerosis. Clin Neuropharmacol 2010;33:91-101.
39. Dev KK, Mullershausen F, Mattes H, et al. Brain sphingosine-1-phosphate receptors: implication for FTY720 in the treatment of multiple sclerosis. Pharmacol Ther 2008;117:77-93.
40. Brinkmann V. FTY720 (fingolimod) in Multiple Sclerosis: therapeutic effects in the immune and the central nervous system. Br J Pharmacol 2009;158:1173-82.
41. Matloubian M, Lo CG, Cinamon G, et al. Lymphocyte egress from thymus and peripheral lymphoid organs is dependent on S1P receptor 1. Nature 2004;427:355-60.
42. Pappu R, Schwab SR, Cornelissen I, et al. Promotion of lymphocyte egress into blood and lymph by distinct sources of sphingosine-1-phosphate. Science 2007;316:295-8.
43. Behrangi N, Fischbach F, Kipp M. Mechanism of Siponimod: Anti-Inflammatory and Neuroprotective Mode of Action. Cells 2019;8.
44. Lublin F, Miller DH, Freedman MS, et al. Oral fingolimod in primary progressive multiple sclerosis (INFORMS): a phase 3, randomised, double-blind, placebo-controlled trial. The Lancet 2016;387:1075-1084.
45. Van Doorn R, Van Horssen J, Verzijl D, et al. Sphingosine 1-phosphate receptor 1 and 3 are upregulated in multiple sclerosis lesions. Glia 2010;58:1465-76.
46. Novgorodov AS, El-Alwani M, Bielawski J, et al. Activation of sphingosine-1-phosphate receptor S1P5 inhibits oligodendrocyte progenitor migration. Faseb j 2007;21:1503-14.
47. Tham CS, Lin FF, Rao TS, et al. Microglial activation state and lysophospholipid acid receptor expression. Int J Dev Neurosci 2003;21:431-43.
48. Gentile A, Musella A, Bullitta S, et al. Siponimod (BAF312) prevents synaptic neurodegeneration in experimental multiple sclerosis. J Neuroinflammation 2016;13:207.

49. Jackson SJ, Giovannoni G, Baker D. Fingolimod modulates microglial activation to augment markers of remyelination. J Neuroinflammation 2011;8:76.
50. O'Sullivan C, Schubart A, Mir AK, et al. The dual S1PR1/S1PR5 drug BAF312 (Siponimod) attenuates demyelination in organotypic slice cultures. J Neuroinflammation 2016;13:31.
51. National Institute for Clinical Excellence (NICE). Disease-modifying therapies for multiple sclerosis. https://pathways.nice.org.uk/pathways/multiple-sclerosis#path=view%3A/pathways/multiple-sclerosis/disease-modifying-therapies-for-multiple-sclerosis.xml&content=view-index. Accessed 05-Mar-2019.
52. National Institute for Clinical Excellence (NICE). Beta interferons and glatiramer acetate for treating multiple sclerosis. Technology appraisal guidance [TA527]. https://www.nice.org.uk/guidance/ta527. Accessed 06-Mar-2019.
53. La Mantia L, Vacchi L, Rovaris M, et al. Interferon beta for secondary progressive multiple sclerosis: a systematic review. J Neurol Neurosurg Psychiatry 2013;84:420-6.
54. Panitch H, Miller A, Paty D, et al. Interferon beta-1b in secondary progressive MS: results from a 3-year controlled study. Neurology 2004;63:1788-95.
55. National Institute for Clinical Excellence (NICE). Ocrelizumab for treating relapsing-remitting multiple sclerosis. Technology appraisal guidance [TA533]. https://www.nice.org.uk/Guidance/TA533. Accessed 06-Mar-2019.
56. National Institute for Clinical Excellence (NICE). Ocrelizumab for treating primary progressive multiple sclerosis. Technology appraisal guidance [TA585]. https://www.nice.org.uk/guidance/ta585. Accessed 12-Jun-2019.
57. National Institute for Clinical Excellence (NICE). Cladribine tablets for treating relapsing-remitting multiple sclerosis. Technology appraisal guidance [TA493]. https://www.nice.org.uk/Guidance/TA493. Accessed 06-Mar-2019.
58. European Medicines Agency. Summary of Product Characteristics - Interferon beta-1a (Rebif). https://www.ema.europa.eu/en/documents/product-information/rebif-epar-product-information_en.pdf. Accessed 05-Mar-2019.
59. NHS England. Treatment Algorithm for Multiple Sclerosis Disease-modifying Therapies. https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2019/03/Treatment-Algorithm-for-Multiple-Sclerosis-Disease-Modifying-Therapies-08-03-2019-1.pdf. Accessed 28-Mar-2019.
60. Shirani A, Okuda DT, Stuve O. Therapeutic Advances and Future Prospects in Progressive Forms of Multiple Sclerosis. Neurotherapeutics 2016;13:58-69.
61. Novartis Data on File. SPECTRUM Healthcare Professionals Survey.
62. Kapoor R, Ho PR, Campbell N, et al. Effect of natalizumab on disease progression in secondary progressive multiple sclerosis (ASCEND): a phase 3, randomised, double-blind, placebo-controlled trial with an open-label extension. Lancet Neurol 2018;17:405-415.
63. Novartis Data on File. Interim CSR (Core Part) for siponimod (BAF312), 2014.
64. Novartis Data on File. Clinical Study Report Amendment. 2018.
65. Novartis Data on File. BAF312A in multiple sclerosis. Statistical Overview. . 2018.
66. Novartis Data on File. Delay in time to CDP data. 2018.

67. Polman CH, Reingold SC, Banwell B, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. Ann Neurol 2011;69:292-302.
68. Hobart JC, Riazi A, Lamping DL, et al. Measuring the impact of MS on walking ability: the 12-Item MS Walking Scale (MSWS-12). Neurology 2003;60:31-6.
69. Motl RW, Snook EM. Confirmation and extension of the validity of the Multiple Sclerosis Walking Scale-12 (MSWS-12). J Neurol Sci 2008;268:69-73.
70. Hobart J, Cano S. Improving the evaluation of therapeutic interventions in multiple sclerosis: the role of new psychometric methods. Health Technol Assess 2009;13:iii, ix-x, 1-177.
71. EXPAND Clinical Study Record. https://clinicaltrials.gov/ct2/show/NCT01665144. Accessed 23-Apr-2019.
72. O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. Biometrics 1979;35:549-56.
73. Kragt JJ, van der Linden FA, Nielsen JM, et al. Clinical impact of 20% worsening on Timed 25-foot Walk and 9-hole Peg Test in multiple sclerosis. Mult Scler 2006;12:594-8.
74. Rudick RA, Polman CH, Cohen JA, et al. Assessing disability progression with the Multiple Sclerosis Functional Composite. Mult Scler 2009;15:984-97.
75. Barin L, Vaney C, Puhan MA, et al. Recommended outcome measures for inpatient rehabilitation of multiple sclerosis are not appropriate for the patients with substantially impaired mobility. Mult Scler Relat Disord 2018;22:108-114.
76. Bethoux F, Bennett S. Evaluating walking in patients with multiple sclerosis: which assessment tools are useful in clinical practice? Int J MS Care 2011;13:4-14.
77. Dolan P. Modeling valuations for EuroQol health states. Med Care 1997;35:1095-108.
78. LaRocca NG, Hudson LD, Rudick R, et al. The MSOAC approach to developing performance outcomes to measure and monitor multiple sclerosis disability. Mult Scler 2018;24:1469-1484.
79. Benedict RH, Bruce J, Dwyer MG, et al. Diffusion-weighted imaging predicts cognitive impairment in multiple sclerosis. Mult Scler 2007;13:722-30.
80. Benedict RHB, Fox R, Tomic D, et al. Effect of Siponimod on Cognition in Patients with Secondary Progressive Multiple Sclerosis (SPMS): Phase 3 EXPAND Study Subgroup Analysis (S44.005). Presented at AAN 2019.
81. European Medicines Agency. ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials. https://www.ema.europa.eu/en/documents/scientific-guideline/draft-ich-e9-r1-addendum-estimands-sensitivity-analysis-clinical-trials-guideline-statistical_en.pdf. Accessed 30-May-2019.
82. SPECTRIMS MS Study Group. Randomized controlled trial of interferon-beta-1a in secondary progressive MS: Clinical results. Neurology 2001;56:1496-504.
83. Li DK, Zhao GJ, Paty DW. Randomized controlled trial of interferon-beta-1a in secondary progressive MS: MRI results. Neurology 2001;56:1505-13.
84. European Study Group. 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 1998;352:1491-7.
85. Kappos L, Polman C, Pozzilli C, et al. Final analysis of the European multicenter trial on IFNbeta-1b in secondary-progressive MS. Neurology 2001;57:1969-75.
86. Cohen JA, Cutter GR, Fischer JS, et al. Benefit of interferon beta-1a on MSFC progression in secondary progressive MS. Neurology 2002;59:679-87.
87. National Institute for Clinical Excellence (NICE). NICE DSU Technical Support Document 18: Methods for Population-Adjusted Indirect Comparisons in Submissions to NICE. http://nicedsu.org.uk/wp-content/uploads/2018/08/Population-adjustment-TSD-FINAL-ref-rerun.pdf. Accessed 22-Mar-2019., 2016.
88. Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. Stat Med 2009;28:3083-107.
89. Institute for Clinical and Economic Review (ICER). Siponimod for the Treatment of Secondary Progressive Multiple Sclerosis: Effectiveness and Value. https://icer-review.org/wp-content/uploads/2018/10/ICER_MS_Evidence_Report_050219.pdf. Accessed 11-Jun-2019. 2019.
90. European Medicines Agency. Summary of Product Characteristics - Avonex. https://www.ema.europa.eu/en/documents/product-information/avonex-epar-product-information_en.pdf. Accessed 30-May-2019.
91. EXCHANGE Clinical Study Record. https://clinicaltrials.gov/ct2/show/NCT03623243. Accessed 23-Apr-2019.
92. Ghezzi A, Amato MP, Makhani N, et al. Pediatric multiple sclerosis: Conventional first-line treatment and general management. Neurology 2016;87:S97-s102.
93. Merck Europe B.V. Mavenclad Summary of Product Characteristics. https://www.ema.europa.eu/documents/product-information/mavenclad-epar-product-information_en.pdf. Accessed 21-May-2019.
94. Roche Products Limited. Ocrevus Summary of Product Characteristics. Available at: https://www.ema.europa.eu/documents/product-information/ocrevus-epar-product-information_en.pdf. Accessed 21-May-2019.
95. Davies F, Edwards A, Brain K, et al. 'You are just left to get on with it': qualitative study of patient and carer experiences of the transition to secondary progressive multiple sclerosis. BMJ Open 2015;5:e007674.
96. Morrow SA, Drake A, Zivadinov R, et al. Predicting loss of employment over three years in multiple sclerosis: clinically meaningful cognitive decline. Clin Neuropsychol 2010;24:1131-45.
97. Kavaliunas A, Danylaite Karrenbauer V, Gyllensten H, et al. Cognitive function is a major determinant of income among multiple sclerosis patients in Sweden acting independently from physical disability. Mult Scler 2019;25:104-112.
98. Motl RW, Cohen JA, Benedict R, et al. Validity of the timed 25-foot walk as an ambulatory performance outcome measure for multiple sclerosis. Mult Scler 2017;23:704-710.
99. Office for National Statistics. Ethnicity and National Identify in England and Wales: 2011.

https://www.ons.gov.uk/peoplepopulationandcommunity/culturalidentity/ethnicity/articles/ethnicityandnationalidentityinenglandandwales/2012-12-11. Accessed 26-Mar-2019. 2012.
100. National Institute for Clinical Excellence (NICE). Natalizumab for the treatment of adults with highly active relapsing-remitting multiple sclerosis. Technology appraisal guidance [TA127]. https://www.nice.org.uk/guidance/ta127. Accessed 12-Apr-2019.
101. National Institute for Health and Clinical Excellence (NICE). Fingolimod for the treatment of highly active relapsing-remitting multiple sclerosis. Technology appraisal guidance [TA254]. https://www.nice.org.uk/guidance/ta254. Accessed 05-Mar-2019.
102. National Institute for Clinical Excellence (NICE). Teriflunomide for treating relapsing-remitting multiple sclerosis. Technology appraisal guidance [TA303]. https://www.nice.org.uk/guidance/ta303. Accessed 12-Apr-2019.
103. National Institute for Clinical Excellence (NICE). Alemtuzumab for treating relapsing-remitting multiple sclerosis. Technology appraisal guidance [TA312]. https://www.nice.org.uk/guidance/ta312. Accessed 11-Apr-2019.
104. National Institute for Clinical Excellence (NICE). Dimethyl fumarate for treating relapsing-remitting multiple sclerosis. Technology appraisal guidance [TA320]. https://www.nice.org.uk/guidance/ta320. Accessed 12-Apr-2019.
105. National Institute for Clinical Excellence (NICE). Daclizumab for treating relapsing–remitting multiple sclerosis Technology appraisal 441 [TA441]. https://www.nice.org.uk/guidance/ta441. Accessed 06-June-2019.
106. 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 2015;15:273-9.
107. National Institute for Clinical Excellence (NICE). Guide to the methods of technology appraisal 2013. https://www.nice.org.uk/process/pmg9/resources/guide-to-the-methods-of-technology-appraisal-2013-pdf-2007975843781. Accessed 26-Apr-19.
108. Patzold U, Pocklington PR. Course of multiple sclerosis. First results of a prospective study carried out of 102 MS patients from 1976-1980. Acta Neurol Scand 1982;65:248-66.
109. Pokorski RJ. Long-term survival experience of patients with multiple sclerosis. J Insur Med 1997;29:101-6.
110. Andersen O, Elovaara I, Farkkila M, et al. Multicentre, randomised, double blind, placebo controlled, phase III study of weekly, low dose, subcutaneous interferon beta-1a in secondary progressive multiple sclerosis. J Neurol Neurosurg Psychiatry 2004;75:706-10.
111. European Medicines Agency. Use of multiple sclerosis medicine Lemtrada restricted while EMA review is ongoing. https://www.ema.europa.eu/en/news/use-multiple-sclerosis-medicine-lemtrada-restricted-while-ema-review-ongoing Accessed 06-June-19. 2019.
112. Palace J, Bregenzer T, Tremlett H, et al. UK multiple sclerosis risk-sharing scheme: a new natural history dataset and an improved Markov model. BMJ Open 2014;4:e004073.
113. Office for National Statistics. National life tables, United Kingdom. 2015-2017. https://www.ons.gov.uk/file?uri=/peoplepopulationandcommunity/birthsdeaths

andmarriages/lifeexpectancies/datasets/nationallifetablesunitedkingdomreferencetables/current/nltuk1517reg.xls. Accessed 12-Apr-2019.
114. Koch-Henriksen N, Bronnum-Hansen H, Stenager E. Underlying cause of death in Danish patients with multiple sclerosis: results from the Danish Multiple Sclerosis Registry. J Neurol Neurosurg Psychiatry 1998;65:56-9.
115. Harding KE, Liang K, Cossburn MD, et al. Long-term outcome of paediatric-onset multiple sclerosis: a population-based study. J Neurol Neurosurg Psychiatry 2013;84:141-7.
116. Ruutiainen J, Viita AM, Hahl J, et al. Burden of illness in multiple sclerosis (DEFENSE) study: the costs and quality-of-life of Finnish patients with multiple sclerosis. J Med Econ 2016;19:21-33.
117. Acaster S, Perard R, Chauhan D, et al. A forgotten aspect of the NICE reference case: an observational study of the health related quality of life impact on caregivers of people with multiple sclerosis. BMC Health Services Research 2013;13:346.
118. National Institute for Clinical Excellence (NICE). Donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease. Technology appraisal guidance [TA217]. https://www.nice.org.uk/guidance/ta217. Accessed 12-Apr-2019.
119. Department of Health. NHS reference costs 2017/18. https://improvement.nhs.uk/documents/1973/2_-_National_schedule_of_reference_costs_v2.xlsx. Accessed 15-Apr-2019.
120. Curtis L. BA. PSSRU Unit Costs of Health and Social Care 2018. https://kar.kent.ac.uk/70995/. Accessed 15-Apr-2019.
121. Tyas D, Kerrigan J, Russell N, et al. The distribution of the cost of multiple sclerosis in the UK: how do costs vary by illness severity? Value Health 2007;10:386-9.

Novartis Pharmaceuticals UK Limited
200 Frimley Business Park
Camberley, Surrey
GU16 7SR

NICE
10 Spring Gardens
London
SW1A 2BU

16th October 2019

Single technology appraisal

Siponimod for treating secondary progressive multiple sclerosis [ID1304]

Dear Ross,

Thank you for the opportunity to respond to the clarification questions (CQs) posed by the Evidence Review Group, Warwick Evidence, regarding the Novartis submission for siponimod [ID1304]. Responses to the clarification questions are provided below, and please note:

- Additional data have been provided in order to address the clarification questions, some of which are Academic In Confidence (AIC). These data have been highlighted using underlining and [redacted]. Any figures that are AIC are indicated by a yellow outline.
- Two versions of the responses have been provided: one with AIC clearly marked, and one with this information redacted.
- A checklist of confidentiality information for the clarification questions has been provided as a separate document.
- The additional references requested are provided as PDFs in a separate ERG CQs Reference Pack file.

If you require any further information, please let me know.

Yours sincerely,

Michel Kroes

Health Economics & Outcomes Research Manager
Phone: +44 7867 373612
Email: michel.kroes@novartis.com

Literature searching

1. Please can the company supply the following documents which were missing from the reference pack:

    a. # 14 'Novartis Data on File (Caseby SCL; Montgomery SM; Woodhouse FA; Kroes MK). [Manuscript under development] Transition to secondary progressive multiple sclerosis: the consequences for patients and healthcare systems, a healthcare professional survey 2019.'

A draft of this manuscript is provided in the ERG CQs Reference Pack (SPMS Survey Manuscript Draft) and should be treated as AIC.

    b. # 65 'Novartis Data on File. BAF312A in multiple sclerosis. Statistical Overview. 2018'

The relevant pages of this Novartis Data on File reference are provided in the ERG CQs Reference Pack, and should be treated as AIC.

    c. # 61 'Novartis Data on File. SPECTRUM Healthcare Professionals Survey'.

An abstract detailing this SPECTRUM Healthcare Professionals Survey has been accepted for presentation at the MS Trust Conference (3rd November 2019). Please see this abstract provided in the ERG CQs Reference Pack, which should be treated as AIC until the date of the conference.

    d. # 82 'Novartis Data on File. SCE Appendix (Integrated Summary of Efficacy, data analyses) for siponimod (BAF312), 2018'.

The relevant pages of this Novartis Data on File reference are provided in the ERG CQs Reference Pack, and should be treated as AIC.

Section A: Clarification on effectiveness data

A1. The ERG note the following definition in CS Document B pg.16 "*Implementation of the definition of SPMS in practice can vary widely due to there being no clear clinical, imaging, immunologic, or pathologic criteria to determine a so-called "transition point" when RRMS converts to SPMS – this reflects the fact that RRMS and SPMS form a continuum.*" Can the company please clarify how SPMS was diagnosed and defined in the pivotal trial (Kappos 2018) and defined in the CS, for example criteria and tools used?

The full eligibility criteria for EXPAND are detailed in the Company Submission (CS) Appendix L, Table 105, Pages 588−592. This details how SPMS was diagnosed and defined: [1]

- SPMS was defined by a progressive increase in disability (of at least 6 months duration) in the absence of relapses or independent of relapses[2, 3]

- Attestation by the investigator in a written statement was required that the disease had entered the progressive stage (according to the study definition) at least 6 months prior to enrolment

To be eligible for the EXPAND trial in SPMS, patients also needed to have: [1]

- Disability status at screening with an EDSS score of 3.0 to 6.5 (inclusive)
- Documented EDSS progression in the 2 years prior to the study of ≥1 point for patients with EDSS <6.0 at screening, and ≥0.5 point for patients with EDSS ≥6.0 at screening.
    - If documented EDSS scores were not available, a written summary of the clinical evidence of disability progression in the previous 2 years, and retrospective assessment of EDSS score from data up to 2 years prior to screening were to be submitted for central review by the adjudication committee.[1] This 'Evidence of Disability Progression Form' documented previous evidence from sources such as previous neurological examination findings and medical history to allow the central adjudication committee to assess if the patient was eligible for the EXPAND trial.
- No evidence of relapse or corticosteroid treatment within 3 months prior to randomisation

<u>Decision Problem</u>

A2. In CS Document B1.1 Table 1, pg.12, comparator(s):

a. The company state "*Interferon β-1b is currently the only option specifically for treatment for patients with SPMS and is therefore considered the most relevant comparator within established clinical management*". The ERG note that there is no evidence to show interferon β-1b to be effective in both active and non-active SPMS. Can the company please provide a citation for this statement to demonstrate that any legitimate comparators have not been excluded?

As discussed in CS Document B Section B.1.3.3, Page 19, interferon β-1b (Extavia®) is the only treatment specifically reimbursed for any patients with SPMS (TA527).[4] The other treatments appraised in TA527, including interferon β-1a (Avonex® and Rebif®) and glatiramer acetate, may have a broad licence for relapsing MS, however are recommended by NICE only for use in relapsing-remitting multiple sclerosis (RRMS) specifically. Similarly, ocrelizumab is licensed for relapsing forms of MS, however the manufacturer did not seek a recommendation from NICE for use in relapsing SPMS; ocrelizumab is therefore recommended by NICE for use in RRMS only (it is also licensed and recommended for PPMS).[5, 6] Lastly, cladribine is licensed for patients with highly active RMS but is only recommended for use in highly active RRMS.[7]

This is reflected in the treatment of SPMS in UK clinical practice; the NHS England Treatment Algorithm for disease-modifying therapies (DMTs) indicates interferon β-1b (Extavia®) as the only recommended option for treating SPMS with active disease, evidenced by relapses.[8]

A recent market research survey indicated that, of the patients identified as SPMS who are prescribed a DMT, they would more commonly be prescribed an injectable therapy than a newer oral therapy, perhaps reflecting the NHS England Treatment Algorithm.[9] The use of DMTs in patients with MS acts to reduce signs of disease activity, which therefore prevents classification of treated patients as Non-Active: lack of observed activity may reflect either treatment success or a Non-Active phenotype. In addition, the market research survey indicated that patients with

SPMS tend to have MRI scans less frequently vs patients with RRMS,[9] meaning signs of activity could go undetected, further complicating the Active vs Non-Active classification. In clinical practice therefore, patients receiving interferon β-1b would be expected to include both those with Active and Non-Active disease.

b. Please can the company provide a citation for the following to confirm that it complies with current UK practice: "*Activity in clinical practice includes MRI activity; the interferon β-1b label wording "evidenced by relapses" reflects practice ~15–20 years ago*"

The Lublin *et al.* 2014 criteria define active disease using clinical and/or imaging criteria, as follows:[10]

- Clinical: relapses, acute or subacute episodes of new or increasing neurologic dysfunction followed by full or partial recovery, in the absence of fever or infection
- Imaging (MRI): occurrence of contrast-enhancing T1 hyperintense or new or unequivocally enlarging T2 hyperintense lesions

The final scope issued by NICE for this appraisal only notes that active disease is 'evidenced by relapses'. Our submission included both 'evidenced by relapses and/or MRI activity' to reflect the Lublin *et al.* criteria above. A recent market research survey confirmed that the Lublin *et al.* criteria are used in clinical practice by consultants and/or MS specialist nurses to determine transition to SPMS.[11]

The focus on 'evidenced by relapses' alone likely arises from the EMA licences of Betaferon® (interferon β-1b, 1995)[12] and Avonex® (interferon β-1a, 1997). The Lublin *et al.* criteria which consider both clinical (i.e. relapses) and imaging (i.e. MRI activity), are more recent (2014), and thus better represent current clinical practice. This use of both clinical and imaging features to define Active SPMS has been recognised by the EMA in more recently licenced drugs, such as ocrelizumab (2018) which is indicated for the treatment of adult patients with 'relapsing forms of multiple sclerosis (RMS) with active disease defined by clinical or imaging features'.

A3. In CS Document B1.1 Table 1, pg.13, subgroups to be considered: the company list the following subgroup "*Active SPMS, as evidenced by relapse and/or MRI activity*". Do the company also consider 'SPMS with non-active disease' (i.e., non-relapsing and/or absence of MRI activity) as a subgroup?

Novartis does not wish to consider 'SPMS with non-active disease' as a subgroup. As discussed below in response to Question A21d, determination of activity in clinical practice is difficult, especially when patients being considered for siponimod would be expected to be treated with a DMT for RRMS. Although such DMTs have not shown the ability to delay progression in SPMS, it would be expected that their anti-inflammatory effect will continue to suppress signs of activity in SPMS and, as such, act as a significant confounder with respect to classification of the disease phenotype as Active or Non-Active: a patient with Non-Active disease at baseline may develop activity during a clinical trial, meaning it is not possible to define a subgroup *a priori* with 100% certainty, resulting in inaccurate or uninterpretable efficacy results for a Non-Active SPMS subgroup population.

The anticipated licence for siponimod is 'treatment of adult patients with secondary progressive multiple sclerosis'. As detailed in CS Document B, Section B.2.7.2, Page 58, there was uncertainty at the point of submission as to the final licenced population for siponimod. A specific

subgroup population of Active SPMS was additionally presented, to align with the US FDA licence for siponimod in Active SPMS patients.

Clinical effectiveness

A4. In CS Document B.1.3.1 pg.15-16, the company state "*The disease courses of MS can be seen as a continuum incorporating an intense focal inflammatory component in early RRMS and more neurodegenerative features alongside chronic inflammation and axon loss in progressive forms of MS (SPMS and PPMS) (Figure 1). Nonetheless, both inflammation and neurodegeneration are present in all forms of the disease.*" Siponimod has been approved by the FDA in adults with active SPMS only (not non-active). Can the company please provide the proportion of non-active SPMS patients from the total number of SPMS patients in the pivotal EXPAND trial?

The number and proportions of patients with Non-Active SPMS in the EXPAND trial are as follows:

- [redacted] of the 1,099 patients ([redacted]%) in the Full Analysis Set (FAS; excludes 6 randomised patients from the 1,105 intention-to-treat [ITT] patients: 5 did not receive siponimod following randomisation, 1 did not sign the informed consent form [see Figure 1 in Kappos et al. 2018 EXPAND trial publication])[13] in the siponimod group are Non-Active SPMS
    - [redacted] of the 1,099 patients in the FAS in the siponimod group could not be classified as either Active or Non-Active due to missing baseline characteristics for either relapse history or MRI
- [redacted] of 546 patients ([redacted]%) in the FAS (equal to ITT) in the placebo group are Non-Active SPMS
    - [redacted] of 546 patients in the FAS in the placebo group could not be classified as either Active or Non-Active due to missing baseline characteristics for one or other of relapses history or MRI
    - The ratio of siponimod to placebo patients reflects the 2:1 randomisation of the overall trial.
- In total, [redacted] of the 1,651 patients ([redacted]%) in the EXPAND trial are Non-Active SPMS, 39 are unclassifiable with respect to activity at baseline and 6 were excluded from the FAS and not analysed with respect to subgroup.

A5. In CS Document B.1.3.3 pg.19, the company provides the current treatment pathway and position of siponimod, and state "*interferon β-1b reduces relapse risk in patients with SPMS but has not been shown to be able to significantly slow disability progression versus placebo*". The ERG note the same statement could be made for interferon β-1a drugs as three RCTs (SPECTRIMS, Nordic SPMS, and IMPACT trials) showed the drugs failed to slow disability progression (on EDSS) in SPMS. The ERG note that interferon β-1a and interferon β-1b reduce relapse risk in patients with SPMS, but have not been shown to be able to significantly slow disability progression versus placebo. Can the company please clarify why interferon β-1a was not considered a treatment option in section B.1.3.3?

Although interferon β-1a is not considered as a relevant comparator for our economic analysis, Avonex® and Rebif® are still considered as treatment options for patients with RRMS in CS Document B Section B.1.3.3, as shown in the footnote of Figure 2 (Page 19).

As discussed in the response to Question A2a above, interferon β-1a (Avonex® and Rebif®)[14, 15] is indicated for patients with relapsing MS. However, NICE TA527 has a narrower recommendation than the full licence, and advises interferon β-1a (Avonex® and Rebif®) should be used for RRMS only. In addition, the label for Rebif® specifically indicates that "efficacy has not been demonstrated in patients with secondary progressive multiple sclerosis without ongoing relapse activity."[16] Only interferon β-1b (Extavia®) is recommended by NICE and the NHS England Treatment Algorithm for patients with SPMS (with continuing relapses).[4, 8] Therefore, Extavia® is the most relevant comparator for the economic analysis, as it reflects the only treatment option available for SPMS in UK clinical practice.

Aside from the question at hand, Novartis notes that the Nordic SPMS Study tested a considerable underdose of interferon β-1a when compared to the licensed product and as such was not considered relevant evidence for this appraisal (as discussed in Question A15).

A6. The ERG note that the EU study group trial (#84) showed that interferon β-1b reduced disability progression, but this was in patients with relapsing/active disease. Can the company please confirm that "*interferon β-1b was unable to significantly slow disability progression compared to placebo*"(CS Document B pg.20) predominantly in patients with non-active (non-relapsing) type of SPMS?

The European study (published by European Study Group 1998 and Kappos 2001)[17, 18] included patients (n=718) with the following eligibility criteria: "As evidence of recent disease activity, [patients] were required to have had either at least two relapses or at least a 1.0-point EDSS increase in the 2 years before the study". Patients therefore represented a mixed population of Active and Non-Active SPMS. Results demonstrated benefit in delaying progression on the EDSS scale for interferon β-1b vs placebo: the proportion of patients with a confirmed 2.0-point EDSS progression was approximately 27% lower for the group treated with interferon β-1b (p=0.032).

The North American study (interferon β-1b vs placebo, published by Panitch 2004)[19] similarly included SPMS patients with a history of relapses and progression (n=939), as per the trial's eligibility criteria: "A history of at least one relapse followed by progressive deterioration sustained". Patient baseline characteristics showed that 517/939 (55.1%) of patients were relapse-free in the two years prior to the study. Therefore, just under half of the population would have recently suffered from relapses; indicating that the population represents a mix of Active and Non-Active SPMS. The results showed that for the total population, there was no significant difference in time to confirmed progression of EDSS scores between patients treated with interferon β-1b and placebo. These results align with those from the SPECTRIMS and IMPACT trials, in which interferon β-1a failed to show benefit on EDSS progression vs placebo in the patient population of both Active and Non-Active SPMS.[20, 21]

Lastly, the systematic review published by La Mantia et al. (2013)[22] for interferon β in SPMS confirmed that treatment with interferon β-1a or interferon β-1b does not delay permanent disability in SPMS. Although there is some evidence of better outcomes in patients who had experienced pre-study relapses (i.e. Active SPMS), we believe the evidence base is not robust enough to confirm that interferon β-1b fails to slow disability progression in Non-Active SPMS

only. There is only strong evidence for the ability of interferon β to reduce relapse risk, rather than disability progression, in both Active and Non-Active SPMS.

A7. In CS Document B B.2, pg.21-22 the company state "*however the apparently* [redacted] *between-group differences at Month 24 compared with Month 12 should be interpreted in light of the small sample size and higher variability at Month 24 due to the event-driven trial design*". Can the company please clarify the definition of both *higher variability* and *event-driven trial design?*

The term 'event-driven trial design' relates to how the EXPAND trial had a time-to-event endpoint. The timing of the primary analysis (i.e. analysis of the double-blind Core Part of the trial) was dependent on observing a pre-specified number of events; in this case, 3-month confirmed disability progression (CDP) events. A variable treatment duration that allows for stopping the study when a pre-specified number of events is observed is more efficient than a study with a fixed treatment period per patient. This event-driven design led to lower patient numbers towards the end of the study.

This is discussed in the Kappos *et al.* 2018 EXPAND publication and CS Document B, Section B.2.4, Table 7, Page 37−38. Patients were recruited to EXPAND over a period of two years, and were followed without time limit until sufficient 3-month CDP events were observed for the whole study. The fixed number was initially planned for a minimum of 374 3-month CDP events. However, more CDP events were observed during the trial than originally expected, and the protocol was amended on 06 October 2015 to also ensure that at least 95% of patients had been randomly assigned to treatment for at least 12 months before the primary analysis was conducted.[13] The duration of the Core Part of the trial was therefore variable for each patient (ranging from 3 years for the first patient randomised, to <1 year for the last patient randomised), since it was terminated irrespective of the duration of individual patient participation. Median exposure to treatment was of 18 months.

Reassignment of treatment groups (potential for "rescue therapy") during the EXPAND trial was also based on CDP events. As discussed in CS Document B (Section B.2.3.3, Table 5, Page 27), patients meeting the event criterion of *6-month* CDP during double-blind treatment were reconsented to either: 1) continue double-blind treatment, 2) switch to open-label siponimod, or 3) stop study treatment while following an abbreviated schedule of assessments and either remain untreated or receive another DMT.

This treatment group reassignment, along with the termination of the Core Part of the trial when the pre-defined number of 3-month CDP events had occurred, led to smaller sample sizes and more variability within treatment groups for patient characteristics at Month 24. The patients remaining in the trial were those who had not reached 6-month CDP, i.e. those who had not experienced substantial progression. The number of patients assessed for each secondary or exploratory endpoint decreased over time, with less than half of the randomised patients being evaluated at Month 24 and beyond. This resulted in a decreasing precision of the estimates at later timepoints.

This is further discussed in CS Document Section B.2.10.1 (Pages 79−80), which details the variable duration of siponimod/placebo exposure for different patients, as the Core Part of the trial was terminated irrespective of individual patient participation, and patients were also given the option to discontinue or change their treatment if reaching 6-month CDP.

- Patients randomised to siponimod had similar mean exposure to double-blind study drug ([redacted]) compared with placebo ([redacted]).
- Most patients in each group (80.4% siponimod, 78.8% placebo) had at least 12 months of exposure to double-blind study drug; however, fewer than 30% of patients in either group had at least 24 months of exposure.

With regards to the higher variability observed specifically in EQ-5D, the standard error (SE) on the estimates are bigger (by approximately 30%) at Month 24 than Month 12, due to the loss of patients as a consequence of the event-driven trial design. Confidence intervals (CIs) for the difference are also bigger in Month 24 as compared to Month 12. This explains why, despite a slightly bigger difference observed, change in baseline in EQ-5D did not reach significance at Month 24 (p=0.0913), while it did at Month 12 (p=0.0392). These data are presented in CSR Amendment Table 14.2-19.2, provided in the ERG CQs Reference Pack.

A8. In CS Document B B.2.3, pg.25, the company use the terms LPFT: last patient first treatment; LPLT: last patient last treatment. Can the company please define these terms?

LPFT (last patient first treatment) is defined as the timepoint at which the last patient started their first dose of siponimod.

LPLT (last patient last treatment) is defined as the timepoint at which the last patient took their final treatment, as part of the core part of the EXPAND trial, prior to the open-label extension. For this particular patient, the exposure to siponimod was 11 months.

A9. **PRIORITY QUESTION** In CS Document B B.2.3 pg.27 Table 5, patient switching:

a. The company state "*Patients with 6-month CDP during double-blind treatment were reconsented to either continue double-blind treatment, switch to open-label siponimod, or stop study treatment while following an abbreviated schedule of assessments and either remain untreated or receive another DMT*." Can the company please clarify how these decisions were made? For example, were patients randomised to these other treatments, and on what basis (e.g., response)

Information on patient re-assignment can be found in the CSR, Page 32. During the Treatment Epoch, patients with 6-month CDP (as defined by EDSS, please see below)could be reassigned to one of the following three options. Patients were counselled and re-consented to ensure an informed decision:

- Continue on the double-blind study treatment assignment (i.e. no change)
- Discontinue double-blind study treatment, complete the End of Treatment visit, and switch to open-label siponimod.
    - These patients underwent dose titration to the 2 mg dose with first dose monitoring, regardless of the dose level at the time of the switch, and continued with the regularly scheduled visits.
- Discontinue double-blind study treatment and start any other MS treatment available in the patient's country, continuing under the abbreviated visit schedule.

For the three options for patients after reaching 6-month CDP, randomised treatment allocation remained blinded until the conclusion of the Core Part of the EXPAND trial. Use of open-label siponimod during the Core Part of the trial was appropriately recorded. The informed consent process was documented at the study site prior to dispensing of the next study drug.

Detection of progression

All available post-baseline EDSS scores (scheduled or unscheduled) were evaluated to assess if the change from baseline met the disability progression criterion. The first EDSS assessment that met the criterion defined the onset of tentative disability progression.

Confirmation of progression

Progression was confirmed if a subsequent scheduled visit at least 6 months after onset showed progression and every EDSS score (scheduled or unscheduled) obtained between the onset and confirmation visits also met the progression criterion. Only the EDSS assessments obtained at scheduled visits (including follow-up visits) and in the absence of relapse (confirmed or unconfirmed) were to be used for confirmation of progression. By definition, a relapse could not last longer than 90 days. If the relapse end date was missing or indicated a duration longer than 90 days, a relapse duration of 90 days was assumed for determining whether the EDSS assessment was obtained in the absence of relapse.

b. Please can the company state how many patients switched to open label and/or how many stopped the treatment altogether and where this information is located in the CSR.

This information is available in Section 10.1.2, Table 10-2, Page 88 of the CSR, and is also shown below (Table 1).

Table 1. Premature discontinuation of double-blind study drug after reaching 6-month CDP

Prematurely discontinued double-blind study drug during Treatment Epoch[a]	Siponimod N=1,105 n (%)	Placebo N=649 n (%)	Total N=1,651 n (%)
Switched to open-label siponimod treatment	[redacted]	[redacted]	[redacted]
Stopped treatment and switched to abbreviated visit schedule (i.e. stopped treatment)	[redacted]	[redacted]	[redacted]
Discontinued Treatment Epoch directly from study drug	[redacted]	[redacted]	[redacted]

Footnotes: [a] Patients who discontinued prematurely from the study drug are defined as patients who have been exposed to the study drug and did not complete the Treatment Epoch on the study drug.
Abbreviations: CDP: confirmed disability progression.

A10. In CS Document B B.2.4 pg.36, the company state "*The study was designed to demonstrate superiority of siponimod to placebo with respect to 3-month CDP*." Can the company clarify why this was done given that a two-sided test was used (which also considers inferiority of the treatment drug)?

The primary objective of the EXPAND trial was "to demonstrate efficacy of siponimod relative to placebo in delaying the time to 3-month CDP". Technically, this would correspond to a one-sided test for superiority of siponimod at a 2.5% alpha-level. This would be equivalent to showing a

difference in favour of siponimod significant at a two-sided alpha-level of 5%. The two-sided terminology was used since historically clinical study results were mostly reported in terms of two-sided p-values with a 5% alpha-level, and could demonstrate superiority or inferiority.

However, Novartis confirms that, as per CSR Section 9.7.5.2 Page 62, the null hypothesis remains as: "The null hypothesis tested that there was no difference in the time to 3-month CDP between the siponimod and placebo group versus the alternative hypothesis that there was a difference between the groups."

A11. **PRIORITY QUESTION** In CS Document B B.2.6 Table 14 and 16, can the company please present between-group differences in the proportions with 95% CIs?

CS Document B Section B.2.6 Table 14 and 16 present the proportion of patients free of T1 Gd-enhancing lesions and free of new or enlarging T2 lesions, respectively, by timepoint. Please see the between-group differences for the proportion of subjects (i.e. siponimod minus placebo) shown in Table 2 below.

Table 2. Proportion of subjects free of MRI lesions activity, by timepoint

Endpoint Timepoint	N=1,099 n/m (%)	N=546 n/m (%)	Difference Siponimod – Placebo (95% CI)
Proportion of subjects free of Gd-enhancing T1 lesions (in this scan)			
Month 12	[redacted]	[redacted]	[redacted]
Month 24	[redacted]	[redacted]	[redacted]
Proportion of subjects free of Gd-enhanced T1 lesions (all post-baseline scans)			
All post-baseline scans	[redacted]	[redacted]	[redacted]
Proportion of subjects free of new or enlarging T2 lesion (in this scan relative to previous scan)			
Month 12 (relative of baseline)	[redacted]	[redacted]	[redacted]
Month 24 (relative to Month 12)	[redacted]	[redacted]	[redacted]
Proportion of subjects free of new or enlarging T2 lesion (all post-baseline scans)			
All post-baseline scans	[redacted]	[redacted]	[redacted]

Footnotes: Full Analysis Set used. n = number of subjects who are free of lesions. At last assessment timepoints, m = number of subjects with at least one post-baseline result; At time-points evaluated on a single MRI scan, m = number of subjects with result in this scan.

A12. In CS Document B, pg.36 Discontinuations: the CS states that [redacted] patients in the siponimod arm and [redacted] patients in the placebo arm had discontinued treatment. However, in the CONSORT diagram (Appendix D, pg. 142), the numbers above refer to patients discontinuing the study instead of treatment (which matches the CONSORT diagram in Kappos 2018). Please could the company clarify if the patients listed above were discontinuing study drug or discontinuing the study?

As detailed in the CSR Section 10.1.2, Table 10-1, Page 87, these figures refer to patients discontinuing the *Treatment Epoch*. This is *study* discontinuation rather than treatment (study drug) discontinuation. Patients who completed the study were defined as:

- Patients who complete Treatment Epoch

- Patients who meet criteria (1) and who discontinue post treatment follow-up Epoch
    - Post treatment follow-up Epoch is defined as: Prematurely discontinued double-blind or open-label treatment and did not want to remain in the study (or) completed on double-blind treatment or open-label siponimod and either chose not to enter the Extension Part, or planned to enter the Extension Part, but would not be able to do so within 1 month

Patients who do not meet above criteria were labelled as discontinuing from the study.

Please disregard the statement in CS Document B, Page 36, and instead refer to Kappos *et al.* 2018 and the CONSORT diagram in CS Appendix D, Page 142. This statement should therefore read: "A higher percentage of siponimod than placebo patients completed the Treatment Epoch (81.7% and 77.7%, respectively), which includes patients who completed on double blind or open-label treatment or who completed the Treatment Epoch on the abbreviated visit schedule."

Please note that this issue is pertinent to questions B2 and B6 below and further data considering the difference between study discontinuation and treatment discontinuation are provided below.

A13. In Document B pg 50-51 regarding SDMT, the CS states "*There was an improvement in the siponimod group at Month 12 and Month 24*", whereas the CSR pg.129 states "*There was no worsening in the siponimod group at Month 12 and Month 24*". Document B provides change from baseline data of 0.14 and 1.12 points, respectively, for the siponimod group at Month 12 and Month 24.

a. The ERG could not locate this data in the CSR. Can the company please clarify the location of this data in the CSR?

Please see response for A13a below, as part of A13c.

b. The ERG note that a change of ≥4 points is reported (Document B p52) as "deemed clinically meaningful". Please could the company clarify the clinically meaningful effect size for SDMT?

Please see response for A13b below, as part of A13c.

c. Please could the company clarify whether a change of this size represents an <u>improvement</u> or if it is <u>no worsening</u>?

These data for the Symbol Digit Modalities Test (SDMT) can be found in the additional Novartis Data on File reference, Siponimod SCE Appendix, provided as a response to Question 1 above. Please see Table 3.2.2−4.2. These data are also presented in the Benedict *et al.* American Academy of Neurology (AAN) 2019 poster.[23]

The Multiple Sclerosis Outcome Assessments Consortium have reported in the literature that "research in MS clearly supports the reliability and validity of this test and recently has supported a responder definition of SDMT change approximating 4 points or 10% in magnitude".[24-26] This has also been supported by analyses establishing benchmark SDMT scores associated with varying levels of vocational disability.[24] As such Novartis stated that a 4-point change is "deemed clinically meaningful".

In total three analyses of SDMT are presented for the EXPAND trial:

1. The exploratory analysis fitted a repeated measures model to the change from baseline SDMT data and provided a comparison of the difference in mean change from baseline between arms

2. A post hoc time-to-event analysis on a 4-point improvement (see Benedict *et al.* 2019 AAN conference poster)[23]

3. A post hoc time-to-event analysis on a 4-point deterioration (see Benedict *et al.* 2019 AAN conference poster)[23]

The results of the three analyses found:

- The difference in mean change from baseline analysis shows a nominally significant difference in favour of siponimod at Month 12 and 24, but the size of the difference in mean change from baseline did not reach the 4-point level. Nonetheless a clear numeric trend is apparent with change from baseline being positive (improvement) and growing over time in the siponimod arm but negative (deterioration) and growing more so over time in the placebo arm.[27] The greater difference between siponimod and placebo at Month 12 and 24 therefore represents a trend to improvement compared with a trend to deterioration.

- The post hoc time-to-event analyses for a 4-point improvement or deterioration, respectively, both found a nominally significant difference favouring siponimod

The conclusion of these analyses was that siponimod had a nominally significant benefit on processing speed, as measured by SDMT.

A14. In CS appendix D Table 12 and pg 83, the company suggest that there were 23 unique studies (97 publications), of which 6 were included (in MAIC) and 17 excluded. Of the 17 excluded, 12 were for just 'treatment' (no reason provided), 3 for not reporting outcome, 1 for unlicensed dose, and 1 for inconsistent outcome definition.

   a. Please can the company provide reasons for those 12 studies which were excluded due to 'treatment' alone?

The SLR was conducted from a global perspective, and therefore had the broadest possible scope and included treatments which 1) may be licensed and reimbursed for treatment of MS in countries other than England or Wales and 2) are experimental treatments still under investigation for MS.

Following the completion of this SLR, the selection of treatments was refined to become relevant to UK practice, therefore excluding drugs such as biotin, simvastatin, rituximab, mitoxantrone, ibedenone, fluoxetine, and masitinibe prior to conducting the MAIC. These treatments are not licensed in the UK for MS, predominantly due to still being at investigational/experimental stages of development.

The 12 studies excluded due to 'treatment' reasons are shown in Table 3.

Table 3. Exclusion of trials from the MAIC due to 'treatment' reasons, which were originally captured in the clinical SLR

Trial Reference	Reason for exclusion
MS-SPI trial	Trial investigated, biotin, which is not licensed for treatment of MS in the UK
MS-STAT trial	Trial investigated simvastatin, which is not licensed for treatment of MS in the UK
Morales 2017	Trial compared a non-relevant comparator, rituximab (which is not licensed for treatment of MS in the UK), against DMTs
Perrone 2014	Trial investigated rituximab, which is not licensed for treatment of MS in the UK
Gunduz 2016	Trial investigated mitoxantrone (which is not licensed for treatment of MS in the UK) vs. cyclophosphamide (which is not licensed for treatment of MS in the UK)
Perini 2006	Trial investigated mitoxantrone (which is not licensed for treatment of MS in the UK) vs. cyclophosphamide (which is not licensed for treatment of MS in the UK)
Mostert 2013	Trial investigated fluoxetine, which is not licensed for treatment of MS in the UK
Vermersch 2012	Trial investigated masitinib, which is not licensed for treatment of MS in the UK
Beutler 1996	Trial investigated cladribine, which is only started as an induction therapy for RRMS in the UK, and not administered while a patient is transitioning to SPMS
Rice 2000	Trial investigated cladribine, which is only started as an induction therapy for RRMS in the UK, and not administered while a patient is transitioning to SPMS
Fernandez 2018	Trial investigated stem cell therapy, which is still under investigation for treatment of MS
Bosco 1997	Trial investigated idebenone, which is not licensed for treatment of MS in the UK

Abbreviations: MS: multiple sclerosis; RRMS: relapsing-remitting multiple sclerosis; SPMS: secondary progressive multiple sclerosis; UK: United Kingdom.

b. Please can the company clarify exactly why biotin, simvastatin, rituximab, mitoxantrone, ibedenone, fluoxetine, masitinibe were searched for and included in the SLR, but later excluded from the MAIC for the reason 'intervention'?

Please see above response for A14a.

<u>MAIC analysis</u>

A15. In CS Document B B.2.9.1 Table 29, can the company please clarify why interferon β-1a (Andersen 2004; ref # 110) is included in the SLR, but not in the list of comparator studies considered for MAIC?

The Andersen *et al.* 2004 study refers to the Nordic SPMS Study. As discussed in CS Appendix D.1.4, Table 18, Page 84, this study investigated an unlicensed regimen of interferon β-1a (22 µg

once weekly), which represented a considerable underdose to the licensed regimen, and was therefore not relevant for inclusion as a comparator in the MAIC. In addition, there was evidence available from the SPECTRIMS study for the licensed dose (22 µg three times weekly), which still allowed a comparison against interferon β-1a.[21]

A16. In Document B B.2.9.4 pg. 74, the company state "*Individual patient data from one trial (i.e. EXPAND) were weighted to match mean baseline characteristics (i.e. aggregate or summary data) as published from the included trials identified in the systematic review.*" As interferon β-1b is manufactured by Novartis we assume that IPD is available for interferon β-1b. Can the company please clarify why aggregate data were used, as opposed to IPD?

Interferon β-1b was developed by Schering AG (now part of Bayer Pharma), and is currently marketed as Betaferon® by Bayer Pharma. Due to a commercial arrangement between the companies, Novartis also markets a brand of interferon β-1b, known as Extavia®.[28] Betaferon and Extavia can be considered the same medicinal product, differing only in brand and commercial terms. Since Novartis did not originally develop interferon β-1b, we do not hold the clinical trial data. Aggregate data were therefore used in the absence of individual patient data (IPD).

A17. **PRIORITY QUESTION** In CS Document B B.2.9.4 pg. 75, the company state "*The matching and adjustment process (propensity score reweighting) for each pairwise comparison is reported in greater detail in Appendix D. Please refer to Section B.2.9.2 and Appendix D for a detailed breakdown of the imbalance in inclusion criteria and baseline patient characteristics between studies.*" The ERG consider that in an anchored ITC, adjustment for purely prognostic variables on top of effect modifiers across trials may lead to overmatching and loss of precision. Can the company please clarify whether efforts to identify such prognostic factors were made and explain the rationale for including them in the weighting regression in light of the possibility of over matching?

Clinical experts experienced in treating patients with SPMS in Canada and the UK were consulted to identify potential treatment effect modifiers, after having been informed about the differences between treatment effect modifiers and prognostic factors. Each clinical expert ranked variables in order of importance/likelihood of impact on treatment efficacy. Rank-ordered responses from each clinician were revised until consensus was reached. Next, data-driven treatment effect modifiers determined by statistical approaches (i.e., univariate regressions regarding the relationship between characteristics and treatment effect, CS Appendix D.1.5, Figures 3 and 4) were compared against the consensus rank-ordered list.

To mitigate the risk of including purely prognostic factors, clinical experts were not provided data on relationships between characteristics and absolute treatment response (i.e., prognostic factors), but only provided data on relationship between characteristics and relative treatment effect (i.e., treatment effect modifiers) during this step.

Revisions, if necessary, were made until consensus was reached among clinical experts and a final rank-ordered list of treatment effect modifiers was generated.

The base-case MAIC results presented (described as "scenario A" in the full results in CS Appendix D.1.6) included all rank-ordered variables. Subsequent analyses (i.e., "scenario B" and onwards) removed one variable at a time, starting with the least important and progressing to the most important covariate. Variables excluded early on in this sequence were at a higher risk of not being treatment effect modifiers (i.e., potentially more or only prognostic). For each scenario, the effect estimates with 95% confidence interval, effective sample size and summaries of the adjusting variables are shown (CS Appendix D.1.6). Thus, the scenario analyses assess the sensitivity of our primary results to possible overmatching and loss of precision.

A18. **PRIORITY QUESTION** Can the company please provide the data to allow the ERG to reproduce the MAIC analysis presented in the CS? This would need to include all codes used.

The codes used for the MAIC analysis are provided in a separate Zip file (Question A18 MAIC Code and Data). Please see details of the content of this Zip file below:

- **readme_MAICs.R** contains all the R code for installing the MAIC package and running MAIC analyses
- **MAICs Folder** contains individual R scripts that are called from within **readme_MAICs.R**
- **dummy_data.csv** contains a dummy data set used by the R code to facilitate test runs of the MAIC analyses.
- **cornerstone-maic-master.tar.gz:**
    - This Zip file contains the source code for the MAIC analyses. This code is not intended to be used interactively by the R user
    - Apart from the source R code, most files contained in this Zip file are utility/helper files (e.g. help files, R markdown scripts)
    - Removing or renaming files in this Zip file is not recommended; doing so may cause errors in the R scripts noted above (e.g. readme_MAICs.R)
    - **R** folder contains the source file used every time a user calls a function from the MAIC package
    - **data** and **data-raw** folders include dummy data used internally for the MAIC (R) package; these are not the same as the data contained in **dummy_data.csv**.
    - All other files may be considered helper files that are executed when the MAIC package is being installed

Although Novartis is committed to transparency, at this stage we are unable to share IPD, as it is uncertain whether Novartis has adequate permissions to share the requested EXPAND IPD with an external party such as NICE or the ERG for the purpose of the technology appraisal.

A19. **PRIORITY QUESTION** In CS Document D, D.1.6 pg.115, Can the company please provide the distribution of regression-based weights/propensity scores used in the MAIC?

As discussed in CS Appendix D.1.6, Pages 115–116, a form of propensity score weighting was used, in which patients in one treatment group (in this case, the EXPAND trial for which IPD are available) are weighted by the inverse odds of being in that group compared to the other treatment group (derived from the competitor trial for which only aggregate data are available).

The propensity score model was estimated using the generalised method of moments based on the aggregate data and IPD.[29]

Figure 1–Figure 8 below show a visual description of the distribution of adjustment weights of Scenario A (i.e., base case; fully matched and adjusted) for the relevant pairwise MAICs, for CDP (Figure 1–Figure 5) and ARR (Figure 6–Figure 8) outcomes. For pairwise comparisons where the comparator trials did not report any of the ranked characteristics (i.e., where only matched and unadjusted comparisons were possible), patients could not be weighted after matching. As such, adjustment weight histograms are not applicable for the following comparison with EXPAND: Betaferon® 250 µg (IFNβ-1b; pooled North American Study and European Study) for the ARR outcome.

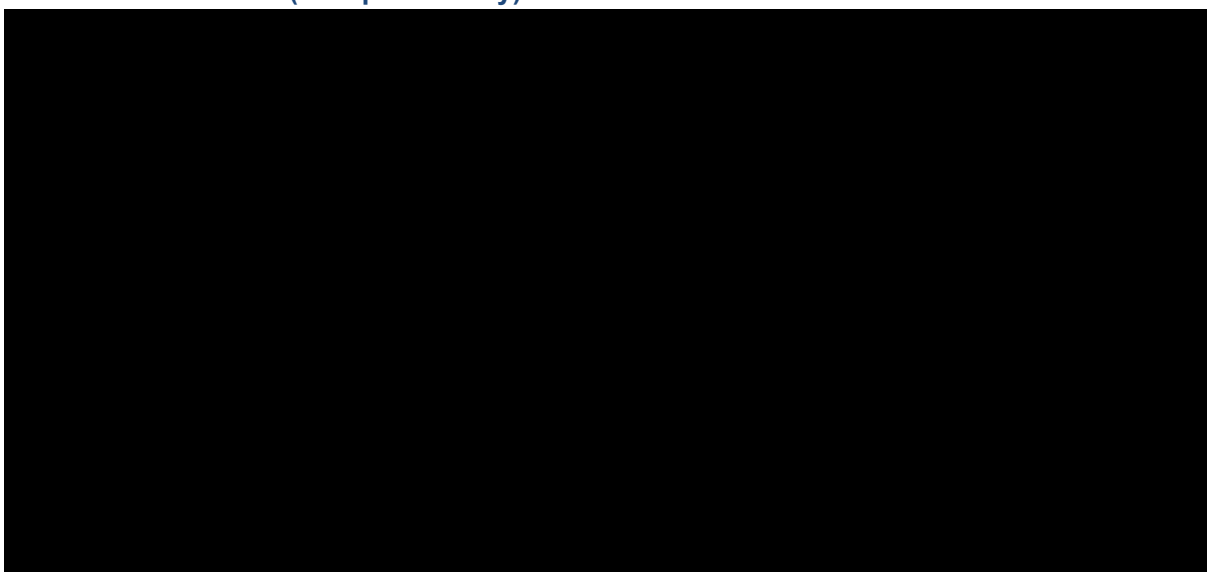
Figure 1: Distribution of adjustment weights for siponimod vs IFNβ-1a (Rebif®) for time to 3-month CDP (SPECTRIMS)

Vertical dashed line represents maximum adjustment weight. The distribution of weights is the same for 22 µg and 44 µg since the same adjustments are made.
Abbreviations: CDP: confirmed disability progression; MAIC: matching-adjusted indirect comparison.

Figure 2: Distribution of adjustment weights for siponimod vs IFNβ-1b (Betaferon®) for time to 6-month CDP (North American Study)

Vertical dashed line represents maximum adjustment weight.
Abbreviations: CDP: confirmed disability progression; MAIC: matching-adjusted indirect comparison.

Figure 3: Distribution of adjustment weights for siponimod vs IFNβ-1b (Betaferon®) for time to 3-month CDP (European Study)

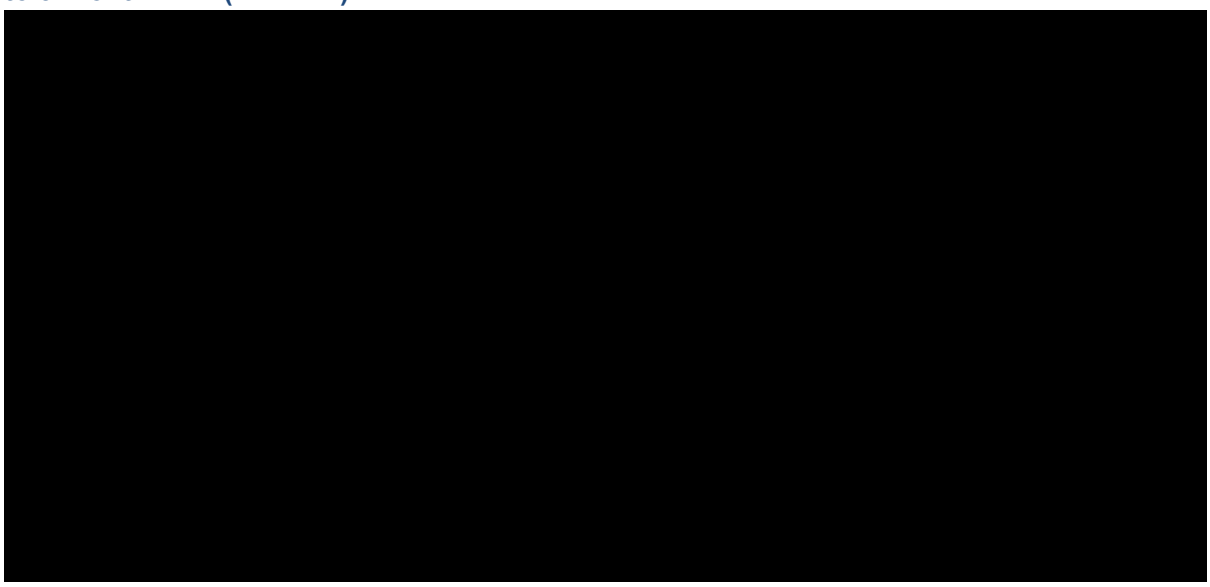


Vertical dashed line represents maximum adjustment weight.
Abbreviations: CDP: confirmed disability progression; MAIC: matching-adjusted indirect comparison.

Figure 4: Distribution of adjustment weights for siponimod vs natalizumab (Tysabri®) for time to 6-month CDP (ASCEND)

Vertical dashed line represents maximum adjustment weight.
Abbreviations: CDP: confirmed disability progression; MAIC: matching-adjusted indirect comparison.

Figure 5: Distribution of adjustment weights for siponimod vs IFNβ-1a (Avonex®) for time to 3-month CDP (IMPACT)



Vertical dashed line represents maximum adjustment weight.
Abbreviations: CDP: confirmed disability progression; MAIC: matching-adjusted indirect comparison.

Figure 6: Distribution of adjustment weights for siponimod vs IFNβ-1a (Rebif®) for ARR (SPECTRIMS)

Vertical dashed line represents maximum adjustment weight. The distribution of weights is the same for 22 µg and 44 µg since the same adjustments are made.
Abbreviations: ARR: annualised relapse rate; MAIC: matching-adjusted indirect comparison.

Figure 7: Distribution of adjustment weights for siponimod vs natalizumab (Tysabri®) for ARR (ASCEND)

Vertical dashed line represents maximum adjustment weight.
Abbreviations: ARR: annualised relapse rate; MAIC: matching-adjusted indirect comparison.

Figure 8: Distribution of adjustment weights for siponimod vs IFNβ-1a (Avonex®) for ARR (IMPACT)

Vertical dashed line represents maximum adjustment weight.
Abbreviations: ARR: annualised relapse rate; MAIC: matching-adjusted indirect comparison.

A20. **PRIORITY QUESTION** In CS Document B, B.2.9.4 pg.75, matching plus adjustment in the MAIC:

a. Can the company please describe the impact of the matching plus adjustment on the CDP and ARR estimates (siponimod vs. placebo) using the EXPAND trial IPD?

The forest plots below (Figure 9−Figure 17) describe the impact of adding each adjustment factor on the CDP and ARR estimates (hazard ratios [HRs] and 95% confidence intervals [CIs]) for siponimod vs placebo.

As described in CS Appendix D.1.6, Page 116, Scenario A adjusts for all ranked characteristics. Subsequent scenarios (i.e. Scenario B onwards) drop the lowest-ranked factor one-by-one from the adjustment; further detail for the scenarios for each comparator trial is provided in Appendix D.1.6.

CDP Outcomes

Figure 9. Effect of matching and adjustment on time to 6-month CDP for siponimod vs placebo with the North American Study (IFNβ-1b)

Scenario A adjusts for all available ranked characteristics, subsequent scenarios drop the least important characteristic from adjustment. Matched sample excludes patients with MS duration <2 years, baseline EDSS <3 or >6.5, and patients with prior IFNβ-1b.
Abbreviations: CDP: confirmed disability progression; CI: confidence interval; EDSS: Expanded Disability Status Score; IFN: interferon

Figure 10. Effect of matching and adjustment on proportion of patients with 6-month CDP at 96 weeks for siponimod vs placebo with ASCEND (natalizumab)

Scenario A adjusts for all available ranked characteristics, subsequent scenarios drop the least important characteristic from adjustment. Matched sample excludes patients >58 years, SPMS onset with previous 2 years of enrolment, baseline EDSS <3 or >6.5, MS severity score of <4, most recent relapses within 3 months, and patients with T25FW test of >30 seconds during screening period.
Abbreviations: CDP: confirmed disability progression; CI: confidence interval; EDSS: Expanded Disability Status Score; T25FW: timed 25-foot walk

Figure 11. Effect of matching and adjustment on time to 3-month CDP for siponimod vs placebo with IMPACT (Avonex®, IFNβ-1a)

Scenario A adjusts for all available ranked characteristics, subsequent scenarios drop the least important characteristic from adjustment. Matched sample excludes with baseline EDSS <3.5 or >6.5, and those with prior IFNβ therapy

Abbreviations: CDP: confirmed disability progression; CI: confidence interval; EDSS: Expanded Disability Status Score; IFN: interferon

Figure 12. Effect of matching and adjustment on time to 3-month CDP for siponimod vs placebo with the European Study (IFNβ-1b)

Scenario A adjusts for all available ranked characteristics, subsequent scenarios drop the least important characteristic from adjustment. Matched sample excludes patients >55 years, baseline EDSS <3 or >6.5, and those with prior IFNβ therapy

Abbreviations: CDP: confirmed disability progression; CI: confidence interval; EDSS: Expanded Disability Status Score; IFN: interferon

Figure 13. Effect of matching and adjustment on time to 3-month CDP for siponimod vs placebo with SPECTRIMS (Rebif®, IFNβ-1a)

Scenario A adjusts for all available ranked characteristics, subsequent scenarios drop the least important characteristic from adjustment. Matched sample excludes patients >55 years old, EDSS <3 or >6.5, and those with prior IFNβ therapy.
Abbreviations: CDP: confirmed disability progression; CI: confidence interval; EDSS: Expanded Disability Status Score; IFN: interferon

ARR Outcomes

Figure 14. Effect of matching and adjustment on ARR for siponimod vs placebo with the North American Study and European Study (IFNβ-1b)

Matched sample excludes patients with baseline EDSS <3 or >6.5, and patients with prior IFNβ therapy.
Abbreviations: ARR: annualised relapse rate; CI: confidence interval; EDSS: Expanded Disability Status Score; IFN: interferon

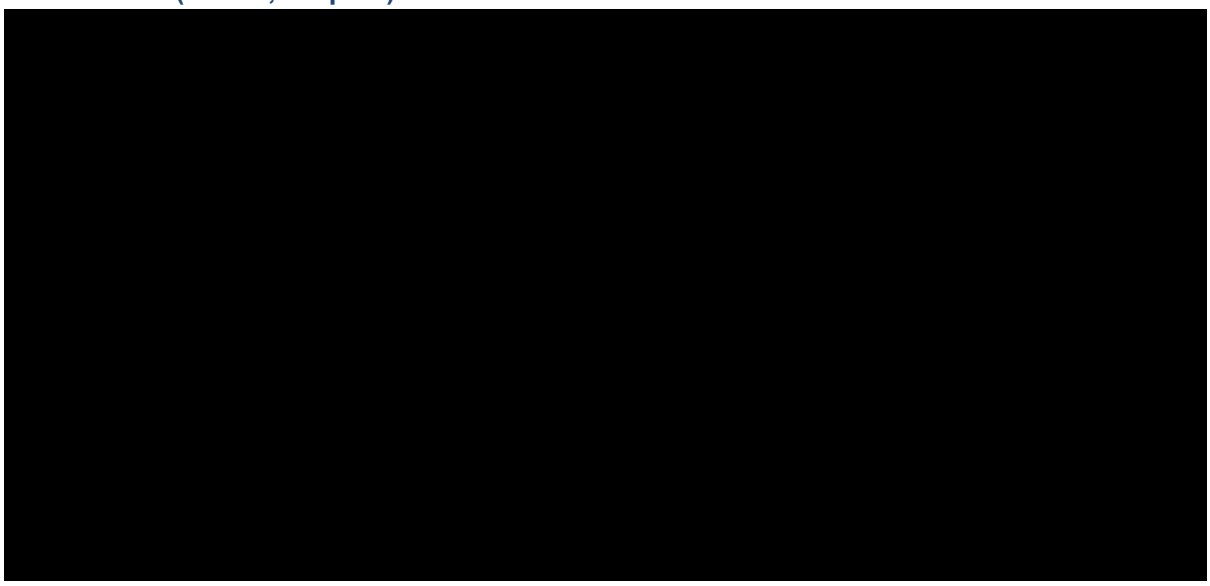
Figure 15. Effect of matching and adjustment on ARR for siponimod vs placebo with ASCEND (natalizumab)

Scenario A adjusts for all available ranked characteristics, subsequent scenarios drop the least important characteristic from adjustment. Matched sample excludes patients >58 years, SPMS onset within previous 2 years of enrolment, baseline EDSS <3 or >6.5, MS severity score of <4, most recent relapses within 3 months, and patients with T25FW test of >30 seconds during screening period.
Abbreviations: ARR: annualised relapse rate; CI: confidence interval; EDSS: Expanded Disability Status Score; T25FW: timed 25-foot walk

Figure 16. Effect of matching and adjustment on ARR for siponimod vs placebo with IMPACT (Avonex®, interferon β-1a)

Scenario A adjusts for all available ranked characteristics, subsequent scenarios drop the least important characteristic from adjustment. Matched sample excludes with baseline EDSS <3.5 or >6.5, and those with prior IFNβ therapy
Abbreviations: ARR: annualised relapse rate; CI: confidence interval; EDSS: Expanded Disability Status Score; IFN: interferon

Figure 17. Effect of matching and adjustment on ARR for siponimod vs placebo with SPECTRIMS (Rebif®, IFNβ-1a)



Scenario A adjusts for all available ranked characteristics, subsequent scenarios drop the least important characteristic from adjustment. Matched sample excludes patients >55 years old, EDSS <3 or >6.5, and those with prior IFNβ therapy.
Abbreviations: ARR: annualised relapse rate; CI: confidence interval; EDSS: Expanded Disability Status Score; IFN: interferon

b. Please can the company provide a comparison table of pre- versus post-matching plus adjustment estimates of CDP and ARR (siponimod vs. placebo) for the EXPAND trial IPD?

Table 4 and Table 5 show the results of the fully matched and adjusted MAIC results for the outcomes of 3- and 6-month CDP and ARR, respectively. The published effect estimates of siponimod vs placebo without matching or adjusting are shown under the column labelled "Published Effect Estimates (95% CI)" and the effect estimate of siponimod vs placebo after matching and adjusting to the comparator trial population are shown under the column labelled "MAIC Results (95% CI)."

Table 4: Summary of MAIC results for 3- and 6-month CDP, CS Document B, Table 41, Page 76

Comparator Intervention	Regimen	Study ID(s)	Published Effect Estimates (95% CI) [c]		MAIC Results (95% CI) [d]	
			Type	Siponimod vs. Placebo	Type	Siponimod vs. Placebo
Time to 6-month CDP						
Betaferon® (SC IFNβ-1b)	250 µg Q2D	North American Study	HR	**0.74 (0.60 to 0.92)**	HR	[redacted]
Proportion with 6-month CDP (96w) [b]						
Natalizumab	300 mg Q4W	ASCEND	OR	[redacted]	OR	[redacted]
Time to 3-month CDP						
Rebif®	22 µg TIW	SPECTRIMS	HR	**0.79**	HR	[redacted]

(SC IFNβ-1a)	44 µg TIW	SPECTRIMS	HR	**(0.65 to 0.95)**	HR	[redacted]
Betaferon® (SC IFNβ-1b)	250 µg Q2D	European Study	HR		HR	[redacted]
Avonex® (IM IFNβ-1a)	*60 µg QW**	IMPACT	HR		HR	[redacted]

Note: An effect size of <1 indicates that the intervention has a favourable outcome relative to the comparator or placebo. Statistically significant values are bolded.
[a] The HR and/or CI were not reported in the publication. Missing values were estimated using either the reported HR and p-value, the reported Kaplan-Meier curve through curve-fitting, or through analysis of IPD, as appropriate.
[b] The proportion of patients who experienced 6-month CDP by 96 weeks based on an increase in EDSS alone. For EXPAND, the proportion of patients with this outcome was calculated using the IPD, based on a conservative assumption that all patients censored at or before 96 weeks had experienced a 6-month CDP event.
[c] Extracted or derived from the EXPAND or comparator publication(s).
[d] The target population is that of the comparator trial.
* This is an unlicensed dose, however the SmPC for Avonex® states that 'no additional benefit has been shown by administering a higher dose (60 µg) once a week.'
Abbreviations: CDP: confirmed disability progression; CI: confidence interval; HR: hazard ratio; IFNβ: interferon beta; IM: intramuscular; IPD: individual patient data; MAIC: matching-adjusted indirect comparison; OR: odds ratio; Q2D: once every other day; QW: once weekly; Q4W: once every four weeks; SC: subcutaneous; TIW: three times weekly.

Table 5: Summary of MAIC results for ARR, CS Document B, Table 42, Page 77

Comparator Intervention	Regimen	Study ID(s)	Published Effect Estimates (95% CI) [a]		MAIC Results (95% CI) [b]	
			Type	Siponimod vs. Placebo	Type	Siponimod vs. Placebo
Betaferon® (SC IFNβ-1b)	250 µg Q2D	North American Study European Study [d]	RR	**0.45 (0.34 to 0.59)**	RR	[redacted]
Rebif® (SC IFNβ-1a)	22 µg TIW	SPECTRIMS	RR		RR	[redacted]
	44 µg TIW	SPECTRIMS	RR		RR	
Natalizumab	300 mg Q4W	ASCEND	RR		RR	[redacted]
Avonex® (IM IFNβ-1a)	60 µg QW*	IMPACT	RR		RR	[redacted]

Note: An effect size of <1 indicates that the intervention has a favourable outcome relative to the comparator or placebo. Statistically significant values are bolded.
[a] Extracted or derived from the EXPAND or comparator publication(s).
[b] The target population is that of the comparator trial.
[c] Error was calculated from the reported RR and p-value.
[d] Error has been estimated using the CI from the North American Study 160 µg/m^2 treatment arm which has a similar effect size and sample size. The Handling Continuous Outcomes in Quantitative Synthesis (Fu et al., 2013) guide recommends that studies only missing error should not be excluded as this can lead to a biased combined estimate.
[e] Matched only (could not adjust).
* This is an unlicensed dose, however the SmPC for Avonex® states that 'no additional benefit has been shown by administering a higher dose (60 µg) once a week.'
Abbreviations: ARR: annualised relapse rate; CI: confidence interval; HR: hazard ratio; IFNβ: interferon beta; IM: intramuscular; Q2D: once every other day; QW: once weekly; Q4W: once every four weeks; RR: rate ratio; SC: subcutaneous; TIW: three times weekly.

A21. **PRIORITY QUESTION** In CS Document B, B.2.9.5 pg.78-79:

a. Based on the MAIC analyses, can the company please clarify it they were able to apply the shared effect modifier assumption to derive or extrapolate the MAIC relative effect estimates to those for the target population?

The results from each MAIC are generalisable to the comparator population included in a given analysis. The estimated treatment effects between active treatments observed in the MAIC should be applicable to any target population under the shared effect modifier assumption which states that the effect modifiers for all active treatments are the same, and the change in treatment effect caused by each effect modifier is the same for all active treatments.

An example to support the shared effect modifier is with respect to the subpopulation of SPMS patients who were relapse-free in the prior 2 years. The proportion of patients who were relapse-free in recent years was also identified as a potential treatment effect modifier for the outcome of CDP. The following example compares EXPAND to SPECTRIMS. The "relapsing" and "non-relapsing" subgroups in SPECTRIMS were defined by whether a patient was relapse-free in the two years before the study and subgroup results were reported for the 44 µg dose. For the outcome of time to 3-month CDP, the HR (95% CI) of Rebif® vs. placebo was [redacted] and [redacted] in the relapsing and non-relapsing subgroups, respectively, demonstrating that the treatment effect was [redacted] in the relapsing subgroup. In EXPAND, for the subgroup created from IPD to match the definition of SPECTIRMS, the HR (95% CI) of siponimod vs. placebo was [redacted] and [redacted] in the relapsing and non-relapsing subgroups, respectively, which demonstrates the same trend wherein the relapsing subgroup has a stronger treatment effect.

Although estimates were not subsequently mapped into another population, the estimated treatment effects between active treatments observed in the MAIC should be applicable to any target population under the shared effect modifier assumption.

b. Can the company please provide a statement of the degree of generalisability of the comparator trial populations in reference to the true target population for the MAIC analyses? In particular, please can the company justify the generalisability to the English SPMS population?

As discussed in CS Document B, Section B.1.3, the transition from predominantly relapsing forms of MS (RMS) to more progressive forms of MS is gradual and the RRMS and SPMS phenotypes inherently overlap. The disease course of MS forms a spectrum; implementation of the definition of SPMS in UK clinical practice varies widely, making the generalisability to the English SPMS population relatively difficult to ascertain. Diagnosis of SPMS tends to be confirmed when disability progression becomes independent of or in absence of relapses, but most healthcare professionals (HCPs) do not use a standardised method to diagnose SPMS. The majority of UK HCPs (60%, n=59) diagnosed SPMS between EDSS 5.5 and 6.5.[11]

Table 6 shows the similarities and differences between EXPAND and the comparator trial baseline populations. When considering the generalisability to the English SPMS population, all the trials include patients diagnosed with MS according to criteria that are used in the UK. The lack of clarity on the definition of SPMS is reflected in the differences in the different trial populations: although differences exist, all are generalisable to somewhere on the spectrum of SPMS diagnosis. None of the trials, including EXPAND, included patients at EDSS 7 or above

and none of the DMTs tested in the trials are anticipated to be used at EDSS 7 or above, in line with UK practice. Mean and median EDSS vary somewhat across the trials, reflecting the lack of a clear transition point between RRMS and SPMS but are broadly in line with majority of UK HCPs diagnosing SPMS between EDSS 5.5 and 6.5.[11] As noted in CS Document B, Section B.2.12, availability of a new active treatment for SPMS is anticipated to shift formal recognition of SPMS earlier in the disease, further enhancing the generalisability to SPMS in the NHS in England.

Table 6: Baseline characteristics in EXPAND and comparator trials

Baseline Patient Characteristics	SPMS					
	EXPAND	ASCEND	North American	IMPACT	European Study	SPECTRIMS
Age (mean years)	48	47.2	46.8	47.6	41	42.8
Proportion female (%)	60	62	63	64	61	63
Mean EDSS score	5.4	5.6	5.1	5.2	5.1	5.4
Proportion of patients with EDSS score ⩾6.0 (%)	56	63	NR	48	45	NR
Time since onset of MS symptoms (mean years)	16.8	16.5	NR	NR	NR	NR
Duration of MS (mean years)	12.6	12.1	14.7	16.5	13.1	13.3
Duration of SPMS (mean years)	3.8	4.8	4	NR	2.2	4
Normalised brain volume (mean cm3)	1423	1423	NR	NR	NR	NR
Proportion of patients with Gd+ lesions of T1-weighted images (%)	21	24	NR	36	NR	NR
Total volume of T2 lesions on T2-weighted images (mean mm3)	15,321	16,793	NR	NR	NR	NR
Proportion of patients without previous use of a DMT (%)	22	23**	NR	NR	NR	NR
Proportion of patients without previous IFN use (%)	37.1	NR	100*	100*	100‡	100*
Mean Timed 25-Foot Walk Test (seconds)	16.7	11.2***	NR	14.5	NR	NR
Time since most recent relapse (months)	59	57	NR	44.4	NR	NR
Proportion of patients relapse-free in prior year (%)	78	84	NR	61	NR	NR
Proportion of patients relapse-free in prior 2 years (%)	64	71	55	NR	30	53
Number of relapses per patient in the prior year (mean)	0.2	NR	NR	0.6	NR	NR
Number of relapses per patient in the previous 2 years (mean)	0.7	NR	0.8	NR	NR	0.9

Green = the characteristic is ≤10% different from that in EXPAND; Red = the characteristic is >10% different from that in EXPAND.
Abbreviations: DMT: disease-modifying therapy; EDSS: expanded disability status scale; IFN: interferon; MS: multiple sclerosis; SPMS: secondary progressive multiple sclerosis.

The European study is the most atypical compared with the other comparator trials, reflecting a younger cohort of patients who are earlier on in their disease progression, with more active disease. These characteristics may explain why the European study met its primary endpoint and

the North American study (studying the same intervention and comparator) failed to meet its primary endpoint, further demonstrating how imbalances in treatment effect modifiers between study populations impact study results. Although all the comparator trials are generalisable to a recognisable SPMS population, imbalances in treatment effect modifiers resulted in the need for the MAIC analysis, as described in CS Document B, Section B.2.9.

c. In CS Document pg. 78, the company state *"Matching was performed to align the population of EXPAND to the reported inclusion and exclusion criteria of trials pertaining to the comparator DMT by excluding EXPAND patients who would not have qualified for the comparator trials, where possible."* Can the company provide a summary of the EXPAND study participants who were excluded on the basis of the matching done in the MAIC? This summary should include the number of patients excluded, their treatment group, summary of their baseline characteristics, and the clinical endpoints of interest (relapse, CDP, discontinuation, etc.).

Table 7 presents the characteristics of the participants of the EXPAND study who were excluded on the basis of the matching conducted in each MAIC analysis, against each comparator trial. The number of total patients excluded after matching is presented, as well as the number of siponimod-treated patients excluded after matching. Baseline characteristics are subsequently presented for all excluded patients.

Table 7: Baseline characteristics of patients in the EXPAND study excluded during the matching conducted in the MAIC

Summary of patients excluded after matching	EXPAND matched to study:					
	SPECTRIMS	North American	European Study	Pooled North American & European Studies	IMPACT	ASCEND
Clinical endpoint of interest	Time to 3-month CDP; ARR	Time to 6-month CDP	Time to 3-month CDP	ARR	Time to 3-month CDP; ARR	Proportion 6-month CDP; ARR
Number of **total** patients excluded after matching, N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of **siponimod-treated** patients excluded after matching, N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline characteristics of excluded patients						
Age, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Female, N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EDSS score, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Time since onset of MS symptoms (years), mean (SD)	[redacted]					
Duration of MS (years), mean (SD)	[redacted]					
Duration of SPMS (years), mean (SD)	[redacted]					
Normalised brain volume (cm^3), mean (SD)	[redacted]					
Patients with Gd-enhancing lesions on T1-weighted images, N (%)	[redacted]					
Number of Gd-enhancing lesions on T1 weighted images, mean (SD)	[redacted]					
Total volume of T2 lesions on T2-weighted images (mm^3), mean (SD)	[redacted]					
Proportion of patients with previous use of a DMT, N (%)	[redacted]					
Proportion of patients with previous IFN use, N (%)	[redacted]					
Timed 25-Foot Walk Test (seconds), mean (SD)	[redacted]					
Time since most recent relapse (years), mean (SD)	[redacted]					
Patients relapse-free in prior year, N (%)	[redacted]					
Patients relapse-free in prior 2 years, N (%)	[redacted]					
Number of relapses per patient in the prior year, mean (SD)	[redacted]					
Number of relapses per patient in the previous 2 years, mean (SD)	[redacted]					
Multiple sclerosis severity score, mean (SD)	[redacted]					

Abbreviations: ARR: annualised relapse rate; CDP: confirmed disability progression; DMT: disease-modifying therapy; IFN: interferon; MS: multiple sclerosis; SD: standard deviation; SPMS: secondary progressive multiple sclerosis.

d. Given the lack of therapies in the subpopulation of non-active/relapse-free SPMS patients (unmet need), can the company please provide a statement regarding whether or not the available evidence (and its limitations) allows them to determine if siponimod exerts any beneficial effect on slowing the progression of disability (CDP) in these non-active/relapse-free SPMS

patients compared to best supportive care (placebo) and the comparator treatments analysed?

The NHS England Treatment Algorithm for DMTs caveats the need to discontinue RRMS DMTs upon confirmation of SPMS (which, as discussed in CS Document B, Section B.3.2.3, Page 98, would usually only be diagnosed in patients with EDSS ≥6.0).[8] As such, patients with SPMS and an EDSS <6.0, who would have qualified for entry into the EXPAND trial and are within the population of this appraisal, are expected to be kept on their RRMS DMT irrespective of a lack of any signs of disease activity. As discussed in response to Question A3 above, determination of activity in clinical practice is difficult, especially when patients being considered for siponimod would be expected to be treated with a DMT for RRMS. Although such DMTs have not shown the ability to delay progression in SPMS, it would be expected that their anti-inflammatory effect will continue to suppress signs of activity in SPMS and, as such, act as a significant confounder with respect to classification of the disease phenotype as Active or Non-Active: a patient with Non-Active disease at baseline may develop activity during the study, meaning it is not possible to define the subgroup *a priori* with 100% certainty, resulting in inaccurate or uninterpretable efficacy results for the Non-Active SPMS subgroup population.

As presented in CS Document B Section B.2.6.7, Pages 52−55, due to relapses acting as an intercurrent event when undertaking CDP analysis and due to the impossibility of defining *a priori* whether any given patient has a Non-Active phenotype, the estimands analysis is to be considered the best approach for determining the relative efficacy of siponimod on CDP vs placebo unaffected by relapses. This sensitivity analysis gave results consistent with the effect on the overall population for 3-month CDP (RR [redacted] vs HR 0.79) and 6-month CDP (RR [redacted] vs HR 0.74). The consistency of these results is indicative that most, if not all, of the effect of siponimod on disability progression is independent of relapses, meaning patients treated with siponimod benefit from the effect of treatment on disability progression irrespective of their relapsing/activity status.

Indirect treatment comparisons between siponimod and other DMTs were not possible in either the “Active” or “Non-Active” subgroups due to a lack of data available to inform the comparisons, as described for the active subgroup in CS Document B Section B.2.9.3, Pages 72–74.

Adverse Events

A22. **PRIORITY QUESTION** In Document B, B.2.10 Adverse Events:

a. In Tables 43-67, the percent numbers (N(%)) do not add up to the total N provided for percent ‘at least one event’. Can the company please clarify the data in these tables, for example how are the percentages calculated and why do they not sum?

CS Document B Section B.2.10.2 Tables 43−48 (Pages 80−85) provide data for treatment-emergent adverse events (TEAEs) in the EXPAND trial. Each patient, in either the siponimod or placebo group, can experience more than one TEAE during the trial, which leads to the n numbers for each TEAE totalling more than the overall n for ‘Number of patients with at least one TEAE’.

The percentages for each TEAE are calculated as a proportion of the *total patient number from the treatment group*, rather than the total patient number experiencing at least one TEAE. For example, for Table 43 (Page 80), 539 patients in the siponimod group experienced an Infection or Infestation, and this was 49.0% of the total patients in the siponimod group (539/1,099*100 = 49.0).

b. In the CS the company provide data on comparative safety of siponimod relative to placebo (EXPAND trial). Can the company please clarify if they compared AEs between siponimod and other active DMTs via MAIC analysis? If so, can they please provide this information?

As detailed in Document B Section B.2.9.5 (Page 78–79), MAICs for the outcome of treatment discontinuation were explored in the feasibility assessment. For all-cause discontinuation, a classical frequentist indirect treatment comparison (ITC) was performed using the Bucher (1997) methods with 95% CIs. All-cause discontinuation was assessed between EXPAND and the included DMT trials as an annualised rate to control for differences in study duration. A MAIC approach corrects for baseline differences in patient populations, allowing for indirect comparison with limited bias when patient level data are available for the index study. However, the baseline characteristics reported in trials are most often related to efficacy outcomes and not safety. Furthermore, treatment effect modifiers related to AEs and discontinuation were not well reported in comparator studies, thereby precluding a valid MAIC. For example, history of gastrointestinal problems may be associated with discontinuations but is not commonly reported in MS studies and cannot therefore be adequately adjusted for. For this reason, Bucher ITCs were performed for safety (i.e., all-cause discontinuation) and no MAIC analysis was undertaken.

c. In Table 48 pg 84, the company provide the number of patients with at least one TEAE causing permanent study drug discontinuation as siponimod (N=1099): [redacted] placebo (N=546) [redacted]. The ERG note that the CSR Table 10-2 pg. 88 states [redacted]Can the company please clarify why these numbers are different?

The figures quoted in CS Document B Section B.2.10.2 Table 48 (Page 84) for TEAEs causing permanent study drug discontinuation are correct, and align with those quoted in Kappos *et al.* 2018, and in Table 12-10 (Page 154) and Table 12-13 (Page 160) of the CSR. These figures relate to serious or clinically significant adverse events (SAFs) leading to study drug discontinuation. The AIC for the figures 84 (7.6%) in the siponimod group and 28 (5.1%) in the placebo group can be disregarded; these can be calculated as the sum of AEs leading to study drug discontinuation in Table 3 of Kappos *et al*.

The figures quoted in Table 10-2 (Page 88) of the CSR relate to all adverse events from the double-blind part of the study leading to study drug discontinuation, rather than the serious or clinically significant adverse events presented above. This explains the slightly higher figure for the siponimod group (n=[redacted] vs n=[redacted]), which arises from the inclusion of further adverse events.

Section B: Clarification on cost-effectiveness data

B1. **PRIORITY QUESTION** The ERG is aware of the evidence report undertaken by the Institute for Clinical and Economic Review (ICER), which is titled 'Siponimod for the treatment of secondary progressive multiple sclerosis: effectiveness and value.' Please can the company clarify or provide justification why this report was not included from the systematic review of the cost-effectiveness evidence? The ERG note that it is referred to on page 91 of the CS Document B (#89).

As detailed in CS Appendix G.1, the cost-effectiveness SLR was first conducted in November 2018, and subsequently updated in April 2019, with the searches run on 30th April 2019. The ICER report was published on 2nd May 2019 and was therefore not captured in the searches due to a later publication date. Additionally, the cost-effectiveness SLR did not include the ICER website as a source for the HTA website of grey literature searching.

B2. **PRIORITY QUESTION** Please can the company provide the individual patient level data for all-cause treatment discontinuation, which were used to fit the fully fitted parametric curves?

As discussed for Question A18 above, at this stage Novartis is unfortunately unable to share IPD. It is uncertain whether Novartis has adequate permissions to share the requested EXPAND IPD for all-cause treatment discontinuation with an external party such as NICE or the ERG for the purpose of the technology appraisal.

However, in lieu of providing IPD, Novartis is able to share the Kaplan–Maier curves and relevant data for both study and treatment discontinuation, please see in the ERG CQs Reference pack *Siponimod_EXPAND_Discontinuation_KMcurves.xlsx*. For adverse events and discontinuation rates, see *Siponimod_EXPAND_AE and Discontinuation Rates.xlsx*. Provision of the Kaplan–Maier data should allow the ERG to recreate pseudo-IPD using the Guyot method common in oncology appraisals;[30] as such, Novartis hopes that the data provided allow the ERG to pursue their intended analysis.

There are two types of discontinuation in EXPAND, study discontinuation (used in the submitted model) and treatment discontinuation. A comparison of study and treatment discontinuation in the EXPAND trial is defined in Table 8.

Table 8 Study and treatment discontinuation of patients in EXPAND

	Study discontinuation	Treatment discontinuation
Definition	Patients who completed study were defined as: 1. Patients who completed treatment epoch[a] 2. Patients meeting criteria (1) and who discontinued post treatment follow-up epoch[b] Patients not meeting above criteria were labelled as discontinuing from the study	The following patients were considered to discontinue treatment based on trial protocol: 1. Patients who receive at least 1 dose of open-label medication in Core part of study 2. Patients not meeting criteria (1) and who enter abbreviated schedule[c] 3. Patients not meeting criteria (1) and (2) above and who

		discontinue treatment epoch on study drug
Censoring time for patients who complete the study	Date of last siponimod dose in study	Date of last siponimod dose in double-blind phase of trial
Time to event	Time to discontinuation for patients who discontinue the study	Time to discontinuation for patients who discontinue the study drug

Footnotes: [a] Treatment Epoch is defined as below in the CSR:
Treatment Epoch represents the Core Part of the study (without the post-treatment Follow-up Epoch)
[b] Post treatment follow-up epoch is defined as below in the CSR:
Prematurely discontinued double-blind or open-label treatment and did not want to remain in the study (or) completed on double-blind treatment or open-label siponimod and either chose not to enter the Extension Part, or planned to enter the Extension Part, but would not be able to do so within 1 month
[c] Abbreviated schedule is defined as below in the CSR:
Patients who had 6-month CDP during the treatment epoch were provided with options that included starting treatment with open-label siponimod as rescue medication. Patients who prematurely discontinue double-blind study drug during the treatment epoch were asked to remain in the study and follow an abbreviated visit schedule

Study discontinuation

Kaplan–Maier curves generated for all-cause study discontinuation are provided in Figure 18 and Figure 19; based on the fitted Kaplan–Maier curves, number of patients discontinuing from study every year and survival probabilities are reported in Figure 19; dotted lines represent 95% confidence intervals. Date of last siponimod dose in the study was considered as the censoring time for patients who complete the study. Frequency of patients completing or discontinuing from the study are detailed in Table 9.

Table 9 Discontinuation of patients from the study

	Siponimod N=1,099*	Placebo N=546	Total N=1645
Subjects completing the study	903 (82.17%)	424 (77.66%)	1,327 (80.67%)
Subjects discontinuing from the study	196[a] (17.83%)	122 (22.34%)	318 (19.33%)

Footnotes: [a] Note that the figure of 197/1,100 includes one patient who was found not to have provided informed consent; 196/1,099 excludes this patient

Figure 18 Cumulative percentage of subjects discontinuing from the study

Figure 19 Kaplan–Maier survival curves for risk of study discontinuation for patients on siponimod and placebo

Based on log-rank test, p-value was 0.04. As p-value for log-rank test is <0.05, there is a significant difference between discontinuation probabilities of siponimod and placebo at the 5% significance level. Log-rank test shows the probability to discontinue study medication prematurely in treatment groups over time.

Treatment discontinuation

In addition to the study discontinuation, treatment discontinuation of patients in the study was analysed in the CSR. Date of last siponimod dose in the double-blind phase of trial was considered as the censoring time for patients who complete the study. Frequency of patients completing or discontinuing treatment are detailed in Table 10.

Table 10 Discontinuation of patients from treatment

	Siponimod N=1099[a]	Placebo N=546	Total N=1645
Subjects completing treatment	[redacted]	[redacted]	[redacted]
Subjects discontinuing treatment	[redacted]	[redacted]	[redacted]

Footnotes: [a] Note that the figure of 1,100 includes one patient who was found not to have provided informed consent; 1,099 excludes this patient

Kaplan–Maier curves were generated for treatment discontinuation and are provided in Figure 20 and Figure 21; based on the fitted Kaplan–Maier curves, number of patients discontinuing from treatment every year and survival probabilities are also provided in Figure 21; dotted lines represent 95% confidence intervals.

Figure 20 Cumulative percentage of subjects discontinued from the treatment

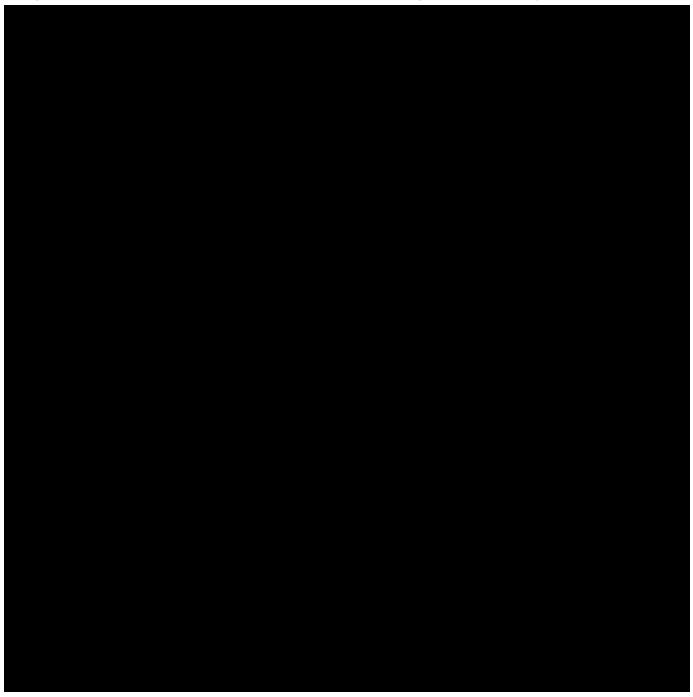


Figure 21 Kaplan–Maier survival curves for risk of treatment discontinuation for patients on siponimod and placebo

Based on log-rank test, p-value was 0.003. As p-value for log-rank test is <0.05, there is a significant difference between discontinuation probabilities of siponimod and placebo at 5% significance level. Log-rank test shows the probability to discontinue study medication prematurely in treatment groups over time.

Summary: study and treatment discontinuation model inputs

Table 11 reports the time-constant discontinuation probability derived by converting 3-year trial discontinuation to annual discontinuation probability. Table 12 reports the parameters for distributions fitted to derive time-dependent discontinuation rates.

Table 11 Time-constant discontinuation for siponimod

Discontinuation for siponimod	n	N	Probability (3-year duration)	Time (in years)	Annual rate	Annual probability
Study	197	1,100	17.91%	3	0.0658	6.37%
Treatment	[redacted]	1,100	[redacted]	3	[redacted]	[redacted]

Table 12 Time-dependent discontinuation rates: Parameters of statistical distributions

Distribution type	Parameter 1	Parameter 2	AIC
Study discontinuation			
Exponential	[redacted]		[redacted]
Weibull	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]
Treatment discontinuation			
Exponential	[redacted]		[redacted]
Weibull	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]

AIC: Akaike information criterion

B3. **PRIORITY QUESTION** The company stated that all patients require a genotype test costing £35 before initiation of siponimod treatment and, in practice this cost will be borne by Novartis. However, in the economic analysis the resource use and costs were incurred by the NHS.

a. Please can the company clarify if these costs will be borne by the company?

As discussed in CS Document B Section B.3.5.1 (Page 114), it was anticipated at the point of submission that Novartis would bear the cost of the genotype test. However, a £35 cost was added to the cost-effectiveness model as a conservative assumption, as it increases the administration costs of siponimod relative to the comparator.

Novartis is now able to confirm that we will provide access to the genotyping service to all NHS Trusts and therefore there is no expected cost to the NHS for this test. An NHS-validated private provider has been selected to provide the service on behalf of Novartis starting January 2020 (subject to siponimod EMA approval).

b. Please clarify if the hypothetical cohort of 1000 people with SPMS reflect those with CYP2C9*2*3 or CYP2C9*1*3 gene?

The hypothetical cohort reflects patients with all polymorphisms eligible for siponimod; patients who are contraindicated from siponimod treatment are not included in the model. There are no efficacy or safety differences between patients on siponimod with 1 mg or 2 mg dose based on the appropriate polymorphism. Hence, no specific percentage split is considered for different polymorphisms in the model.

c. Please can the company clarify the name of the genotype test and its sensitivity and specificity?

For less than ~6 samples per week the analysis will be performed by polymerase chain reaction (PCR) and Sanger sequencing (>99% specificity and sensitivity) of exons 3 and 7 of *CYP2C9.* Once activity increases above this threshold, a Fluorescent Amplification Refractory Mutation System (ARMS) assay (>99% specificity and sensitivity) will be performed.

d. Please can the company clarify what proportion of people with SPMS initiate treatment with siponimod as a result of having the appropriate gene?

The frequency of CYP2C9 polymorphism is highest among Caucasians. Less than 0.5% of the Caucasian population have the 3*3 polymorphism which indicates siponimod should not be initiated. In the company budget impact analysis, 99.60% of SPMS patients are eligible to be treated with siponimod (2 mg) based on having the appropriate CYP2C9 genotype.

e. Can the company clarify if there is counselling before and after receiving the results of the genotype test?

Appropriate guidance and material will be provided to the NHS HCP to introduce the test to patients while collecting the buccal swab. Results from the genotype test will be provided to the NHS HCP, and there will be guidance and support available if a patient is not eligible for siponimod.

The outcome of the test is specifically related to siponimod metabolising status. The test does not indicate any other health risks and as such, broader counselling is not anticipated to be required before or after the test.

B4. **PRIORITY QUESTION** In CS Document B, pg. 99, Table 52 includes the baseline distribution in percentages for an ITT population and an active SPMS population.

a. Using the table below, please can the company provide the numbers from the trial that have been used to derive the percentages for the ITT and active SPMS columns?

Please see response for B4b and Table 13 below.

b. Please can the company provide the characteristics and baseline EDSS distribution in numbers and in percentages for the non-active SPMS group using the additional column added to Table 52 by the ERG?

Table 13 has been amended by Novartis to include both the ITT and FAS.

For the ITT population (N=1,651) mean age and percentage male patient characteristics, as well as the baseline EDSS percentages have been retained. To this has been added EDSS numbers distribution numbers and percentages from the FAS (N=1,645): as noted in the response to Question A4 above, a total of 6 patients who were randomised to siponimod were excluded from the FAS. Of these 6 patients, 5 never received siponimod and 1 did not sign consent prior to initiation of study procedures. The patient who did not sign prior consent was excluded from all analysis sets with the exception of the ITT. Corresponding Active and Non-Active SPMS patient characteristics have also been added to the following table, as noted previously some patients could not be assigned to either subgroup due to missing baseline characteristics (as discussed in the response to Question A4). The distribution of EDSS states is consistent between the two subgroups; if anything, the Non-Active subgroup distribution tends to be slightly lower on the EDSS scale.

Table 13: Patients Characteristics Used in the Model

Characteristic	ITT population N=1,651	FAS N=1,645	Non-active SPMS (n=827)	Active SPMS (N=779)
Mean age (years)	48	NR	[redacted]	[redacted]
% male patients, n (%)	39.9%	NR	[redacted]	[redacted]
Baseline EDSS distribution in percentages (assuming cohort size of 1,000 patients), n(%)				
EDSS 0	0%	0 (0%)	0 (%)	0.00%
EDSS 1	0%	0 (0%)	0 (%)	0.00%
EDSS 2	[redacted]	[redacted]	[redacted]	[redacted]
EDSS 3	[redacted]	[redacted]	[redacted]	[redacted]
EDSS 4	[redacted]	[redacted]	[redacted]	[redacted]
EDSS 5	16.09%	[redacted]	[redacted]	[redacted]
EDSS 6	55.33%	[redacted]	[redacted]	[redacted]
EDSS 7	[redacted]	[redacted]	[redacted]	[redacted]
EDSS 8	0%	0 (0%)	0 (0.00%)	0 (0.00%)
EDSS 9	0%	0 (0%)	0 (0.00%)	0 (0.00%)
Total	**100%**	**100%**	**100%**	**100%**

B5. Please can the company clarify if there is a feature in the economic model that allows for the pairwise comparison between siponimod versus best supportive care, using 6-month disability progression from the MAIC in the ITT population and, also for the comparison between interferon β-1b and best supportive care?

There is no functionality within the company Microsoft Excel cost-effectiveness model allowing the pairwise comparison between siponimod and best supportive care (BSC) given that BSC is not an appropriate comparator, in alignment with the NICE scope: BSC was explicitly removed from the scope comparators list by NICE during the scope consultation. Although BSC is not an appropriate comparator, when patients discontinue treatment, they are modelled to receive BSC. Please note that a comparison between interferon β-1b and BSC is also not possible, given that the cost-effectiveness model is programmed such that siponimod is always the relevant intervention.

B6. In CS Document B, pg. 106, Table 60 reports the time-constant discontinuation probabilities used in the scenario analyses, please can the company clarify that these are incidences rather than probabilities?

Time-constant discontinuation probabilities are reported in CS Document B Section B.3.3.5, Table 60, Page 106. The probability of discontinuing siponimod was obtained from the EXPAND trial, whereby 197 out of 1,100 patients treated with siponimod discontinued by the end of the 3-year trial period. As noted in the response to A12, this figure represents study discontinuation, rather than treatment (study drug) discontinuation, see the response to B2 for further discussion of the types of discontinuation data available.

By assuming that the rate of discontinuation within this 3-year trial period is constant, the 3-year probability of discontinuation is converted to an annual rate and finally an annual probability, which is applied in each model cycle. Please refer to the 'Inputs Repository' worksheet in the company cost-effectiveness model, from cell C596 onwards, and Table 14, where the annual probability of discontinuing siponimod is calculated. Please accept our apologies for the misleading title in J577 of this worksheet, which refers to probabilities as incidences.

Table 14: Annual probability of discontinuation for siponimod

	n	N	Probability of discontinuation over 3-years	Annual rate	Annual probability
Discontinuation on siponimod	197	1100	17.91%	0.0658	6.37%

Probability to rate conversion: probability = 1 – exp(–rate*time)

B7. In CS Document B, pg.106, Table 61 reports the adverse events for siponimod from the EXPAND trial, please can the company clarify that these are 3-year and 1-year incidences of adverse events?

3- and 1-year probabilities of each adverse event occurring are reported in CS Document B, Section B.3.3.6, Table 61, Pages 106−107. Adverse events reported in the EXPAND trial which occurred in ≥5% of patients receiving siponimod were selected for inclusion within the company cost-effectiveness model. By assuming that the rate of each adverse event occurring within this 3-year trial period is constant, the 3-year probability for each adverse event has been converted to an annual probability of an adverse event occurring and applied to each annual model cycle. Please refer to the 'Inputs Repository' worksheet in the economic model, from cell C571 onwards, and Table 15, where these annual probabilities are calculated. Please accept our apologies for the misleading title in J577 of this worksheet, which refers to probabilities as incidences.

Table 15: Adverse events (with >5% during trial period in any arm of trial) of siponimod from EXPAND trial

Adverse event	3-year probability	Annual rate	Annual probability
Headache	[redacted]	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]	[redacted]
Fall	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]
Influenza	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]
Back pain	[redacted]	[redacted]	[redacted]
Alanine aminotransferase level increased	[redacted]	[redacted]	[redacted]
Pain in extremity	[redacted]	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]	[redacted]
Depression	[redacted]	[redacted]	[redacted]

B8. In the Microsoft Excel model, worksheet ‘Costs’, the source of the cost of genotype testing before initiating siponimod is given as ‘Verhoef et al. 2016’. Please can the company provide the PDF for the reference ‘Verhoef et al., 2016’?.

This reference has been provided as a PDF in the ERG CQs Reference Pack.

Section C: Textual clarifications and additional points

C1. In CS Document B, pg. 119, Table 73 the sub-heading in the third column states 'Total LYG'. Please clarify if this is life-years gained or life-years?

Subheadings in Table 73 are currently incorrectly labelled as 'Total LYG' and 'Incremental LYG'. Please instead consider these instances instead to be LY (life-year).

C2. In CS Document B pg, 39, the company state "*Sensitivity analyses to explore the effect of siponimod on CDP, unrelated to the effect on relapses, gave results consistent with the effect on overall population for 3-month CDP ([redacted]) and 6-month CDP ([redacted]).*" Can the company please specify where in the CS the details of this sensitivity analysis are reported?

These sensitivity analyses are the estimands analyses, and are reported CS Document B, Section B.2.6.7, Pages 52−55.

C3. In CS Document B, pg. 51, Data extraction for MSIS-29/EQ5D:

a. For physical score, the following statement is made "*The average over all visits for adjusted mean difference was [redacted], which showed a difference ([redacted]) favouring siponimod.*" The ERG could not locate this information, please can the company clarify where this statement originated from?

These data are from the EXPAND CSR Appendices (Table 14.2−18.2) and Siponimod SCE Appendix (Table 3.2.2−5.11). Please see the PDFs provided in the ERG CQs Reference Pack (these data should be treated as AIC).

b. For psychological score the following statement is made: "*The average over all visits for adjusted mean difference was [redacted], which showed a difference ([redacted]) favouring siponimod.*" The ERG could not locate this information, please can the company clarify where this statement originated from?

These data are from the EXPAND CSR Appendices (Table 14.2−18.2) and Siponimod SCE Appendix (Table 3.2.2−5.11). Please see the PDFs provided in the ERG CQs Reference Pack (these data should be treated as AIC).

c. For EQ-5D the following statement is made: "*The average over all visits for adjusted mean difference was [redacted], which showed a difference ([redacted]) favouring siponimod.*" The ERG could not locate this information, please could the company clarify where the statement originated from?

These data are from the EXPAND CSR Amendment. Please see Table 14.2−19.2 provided in the ERG CQs Reference Pack (these data should be treated as AIC).

References

1. Novartis Data on File. Interim CSR (Core Part) for siponimod (BAF312), 2014.
2. Lublin FD, Reingold SC. Defining the clinical course of multiple sclerosis: results of an international survey. National Multiple Sclerosis Society (USA) Advisory Committee on Clinical Trials of New Agents in Multiple Sclerosis. Neurology 1996;46:907-11.
3. Rovaris M, Confavreux C, Furlan R, et al. Secondary progressive multiple sclerosis: current knowledge and future challenges. Lancet Neurol 2006;5:343-54.
4. National Institute for Clinical Excellence (NICE). Beta interferons and glatiramer acetate for treating multiple sclerosis. Technology appraisal guidance [TA527]. https://www.nice.org.uk/guidance/ta527. Accessed 06-Mar-2019.
5. National Institute for Clinical Excellence (NICE). Ocrelizumab for treating relapsing-remitting multiple sclerosis. Technology appraisal guidance [TA533]. https://www.nice.org.uk/Guidance/TA533. Accessed 06-Mar-2019.
6. National Institute for Clinical Excellence (NICE). Ocrelizumab for treating primary progressive multiple sclerosis. Technology appraisal guidance [TA585]. https://www.nice.org.uk/guidance/ta585. Accessed 12-Jun-2019.
7. National Institute for Clinical Excellence (NICE). Cladribine tablets for treating relapsing-remitting multiple sclerosis. Technology appraisal guidance [TA493]. https://www.nice.org.uk/Guidance/TA493. Accessed 06-Mar-2019.
8. NHS England. Treatment Algorithm for Multiple Sclerosis Disease-modifying Therapies. https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2019/03/Treatment-Algorithm-for-Multiple-Sclerosis-Disease-Modifying-Therapies-08-03-2019-1.pdf. Accessed 28-Mar-2019.
9. Novartis Data on File (Caseby SCL; Montgomery SM; Woodhouse FA; Kroes MK). [Manuscript under development] Transition to secondary progressive multiple sclerosis: the consequences for patients and healthcare systems, a healthcare professional survey 2019.
10. Lublin FD, Reingold SC, Cohen JA, et al. Defining the clinical course of multiple sclerosis: the 2013 revisions. Neurology 2014;83:278-86.
11. Novartis Data on File. SPECTRUM Healthcare Professionals Survey.
12. European Medicines Agency. Summary of Product Characteristics - Betaferon. https://www.ema.europa.eu/en/documents/product-information/betaferon-epar-product-information_en.pdf. Accessed 03-Oct-2019.
13. Kappos L, Bar-Or A, Cree BAC, et al. Siponimod versus placebo in secondary progressive multiple sclerosis (EXPAND): a double-blind, randomised, phase 3 study. Lancet 2018;391:1263-1273.
14. European Medicines Agency. Summary of Product Characteristics - Avonex. https://www.ema.europa.eu/en/documents/product-information/avonex-epar-product-information_en.pdf. Accessed 30-May-2019.
15. European Medicines Agency. Summary of Product Characteristics - Rebif. https://www.ema.europa.eu/en/documents/product-information/rebif-epar-product-information_en.pdf (Accessed 03-Oct-2019).
16. European Medicines Agency. Summary of Product Characteristics - Interferon beta-1a (Rebif). https://www.ema.europa.eu/en/documents/product-information/rebif-epar-product-information_en.pdf. Accessed 05-Mar-2019.
17. European Study Group. 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 1998;352:1491-7.
18. Kappos L, Polman C, Pozzilli C, et al. Final analysis of the European multicenter trial on IFNbeta-1b in secondary-progressive MS. Neurology 2001;57:1969-75.
19. Panitch H, Miller A, Paty D, et al. Interferon beta-1b in secondary progressive MS: results from a 3-year controlled study. Neurology 2004;63:1788-95.

20. Cohen JA, Cutter GR, Fischer JS, et al. Benefit of interferon beta-1a on MSFC progression in secondary progressive MS. Neurology 2002;59:679-87.
21. SPECTRIMS MS Study Group. Randomized controlled trial of interferon- beta-1a in secondary progressive MS: Clinical results. Neurology 2001;56:1496-504.
22. La Mantia L, Vacchi L, Rovaris M, et al. Interferon beta for secondary progressive multiple sclerosis: a systematic review. J Neurol Neurosurg Psychiatry 2013;84:420-6.
23. Benedict RHB, Fox R, Tomic D, et al. Effect of Siponimod on Cognition in Patients with Secondary Progressive Multiple Sclerosis (SPMS): Phase 3 EXPAND Study Subgroup Analysis (S44.005). Presented at AAN 2019.
24. Benedict RHB, DeLuca J, Phillips G, et al. Validity of the Symbol Digit Modalities Test as a cognition performance outcome measure for multiple sclerosis. Multiple Sclerosis Journal 2017;23:721-733.
25. Benedict RHB, Morrow S, Rodgers J, et al. Characterizing cognitive function during relapse in multiple sclerosis. Multiple Sclerosis Journal 2014;20:1745-1752.
26. Morrow SA, Drake A, Zivadinov R, et al. Predicting loss of employment over three years in multiple sclerosis: clinically meaningful cognitive decline. Clin Neuropsychol 2010;24:1131-45.
27. Novartis Data on File. SCE Appendix (Integrated Summary of Efficacy, data analyses) for siponimod (BAF312), 2018.
28. PharmaTimes Website. Novartis gets approval to sell interferon beta-1b in Europe. http://www.pharmatimes.com/news/novartis_gets_approval_to_sell_interferon_beta-1b_in_europe_986982. 2008. Accessed 09-Oct-2019.
29. Signorovitch JE, Wu EQ, Yu AP, et al. Comparative effectiveness without head-to-head trials: a method for matching-adjusted indirect comparisons applied to psoriasis treatment with adalimumab or etanercept. Pharmacoeconomics 2010;28:935-45.
30. Guyot P, Ades AE, Ouwens MJNM, et al. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. BMC Medical Research Methodology 2012;12:9.

NICE National Institute for Health and Care Excellence

Patient organisation submission

Siponimod for treating secondary progressive multiple sclerosis [ID1304]

Thank you for agreeing to give us your organisation's views on this technology 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.

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 a leading patient organisation, representing over the 100,000 people living with MS in the UK. We have 4 national offices and offer a range of services including an award-winning helpline, which provides advice and support to anyone affected by MS.
4b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	None to disclose
5. How did you gather information about the experiences of patients and carers to include in your submission?	We issued a call out to people with secondary progressive MS the MS Society's Research Network, which is made up of hundreds of researchers and people living with MS who sign up to hear about the latest in MS research and input into technology appraisals. For those that responded, we held in-depth telephone interviews.
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?	MS is a complex and unpredictable neurological condition that affects everyone differently. It affects over 100,000 people in the UK. A revised prevalence estimate from Public Health England if expected to be published in 2019. MS is difficult to diagnose, with lots of people waiting 6 months (some significantly longer) from onset of symptoms to receive a formal diagnosis[1]. This is in part due to the fact that the symptoms of MS are varied and mimic other conditions, but also due to the fact that there are different types of MS: • relapsing-remitting MS (RRMS); • primary progressive MS (PPMS); • secondary progressive MS (SPMS). Approximately 50% of people with RRMS will go onto develop SPMS, a form of the condition in which disability gets steadily worse. A patient is no longer likely to have relapses, which are common in RRMS. People living with secondary progressive MS often experience difficulty with their mobility, require the use of mobility aids and experience other symptoms such as speech and cognitive difficulties, fatigue, muscle spasms and chronic pain. A significant number of people living with MS have restricted mobility, finding it difficult to carry out day-to-day activities and require significant support often provided by family and friends. Living with a chronic, progressive condition such as secondary progressive MS is painful, exhausting and disabling. It is also expensive. There are often substantial extra costs, such as accessible transport, specialist equipment, medication and help with household activities – a neurological condition like MS can cost, on average, an additional £200 a week[2]. Research into the burden and cost of MS in the UK has found that this significantly increases with disability progression. One study has found that people at Expanded Disability Status Score (EDSS) 0-3 have related costs of £11,400 per year, while those at EDSS

[1] Peters M, Fitzpatrick R, Doll H et al. (2013) Patients' experiences of health and social care in long-term neurological conditions in England: a cross-sectional survey. Journal of Health Services Research and Policy January 2013 vol. 18 no. pp. 1 28-33.
[2]Extra Costs Commission, Driving down the costs disabled people face : Final report, June 2015, pp. 13

	7-9 have related costs of £36,500 per year (costs factored in all health care and resource utilisation related to MS).[3] **What it is like living with MS** We received many testimonies from people with SPMS which highlighted the difficulties of living with the condition, as well as barriers to engaging in processes such as a NICE Single Technology Appraisal because of difficulties speaking, typing and moving. [redacted], 58, living with secondary progressive MS, described how her MS takes away her independence and severely restricts her ability to interact with people. "I'm stuck in the house and my husband has had to drop his hours to two days a week so that he can be my carer. So unless my friends take me out or my husband, I can't get out of the house." For [redacted], 59, who had a diagnosis of secondary progressive MS in 2007 but experienced symptoms in the early 1990s, is heavily dependent on her partner and has severely restricted mobility, She told us: "200 yards is my absolute max and it varies a lot depending on the climate." Hot or cold temperatures can often affect people with MS significantly. [redacted] has a walking stick which she relies on to move about the house. [redacted] 76, living with secondary progressive MS has great difficulty standing up and moving around. She told us: "I don't have any muscle strength. Getting out of bed can be a problem. I have difficulty moving from an electric chair to an ordinary chair. I am fortunate to park it [wheelchair] at night-time in the bedroom and put it fairly close to the bed which I can use if need to go to the bathroom at night." She talked about the impact her MS has on her. "It is frustrating as I always need help from somebody and am restricted in what I can do. It is really sad because I can no longer handle my money. It takes my independence." Discussing day-to-day impacts she said "I haven't been out in the garden in about three years. It's a simple thing, but it's upsetting". She also spoke about the impact her MS has had on her partner. "I can't do banking online. I rely on [her partner]. He feels upset because he has to know everything about my money."

[3] Thompson et al (2017) *Multiple Sclerosis Journal* Vol. 23 (28) pp. 204-216

	[redacted], 64 living with secondary progressive MS referred to slurred speech, double-vision and "loss of feeling in my fingertips" as common symptoms of his MS. His MS also has a major impact on his walking and mobility. He described day-to-day management as a struggle, saying: "It's bloody difficult. The whole time you think 'Am I going to get through it?'" **Experience of carers** Amongst carers, it was reflected that government agencies do not adequate support them. [redacted], 58 and a carer for her husband, [redacted], living with MS secondary progressive MS, described carers' health and wellbeing being seen as "secondary" telling us: "not only is my husband housebound, so am I. I can't leave him, so I avoid anything that means I have to go out. I forego doctors' appointments, dentist appointments, and anything else that involves me having to leave him." [redacted] described the impact the condition can have on people: "The disease affects everyone differently. My husband is in the final stages of secondary progressive MS. He can no longer get a drink for himself, bathe himself, dress himself or toilet himself. He is bed bound, completely immobile. He has an indwelling catheter (which has caused 3 counts of sepsis, and prolonged hospital stays). As his wife, I handle all his personal care, including medications, catheter care, and bathing". She describes a number of different symptoms that include "pressure sores, brain fog, incontinence (both bladder and bowel), eye sight loss, fatigue, speech problems, memory problems, and lack of mobility." The MS Society carried out an online survey of family and friends of people with MS in the UK (open 1 March-14 June 2019). Of the 549 (self-selecting) respondents, 67% were not in receipt of Carers' Allowance. Like [redacted], they also reported significant strains on their health and wellbeing. A third respondents had experienced depression in the past 12 months as a result of their role supporting someone with MS. A further third said they experienced physical strain; 21% cited loneliness, 27% social isolation; and 20% said that an existing health condition had got worse, as a result of caring.

	In addition, 24% said that they have never had a break from caring and 64% said the person they support gets no other practical support other than from them, placing a huge strain on the individual carer for them and severely limiting employment options. **Impact on Employment** On average people with MS retire from work by the age of 42 due largely to symptoms such as walking difficulties, fatigue and cognitive issues.[4] Only 36% of people with MS are in employment compared with an employment rate of 75% amongst the general population.[5] Of the people who wrote in support of this submission, having to give up work or the fear that they will have to soon was one of the most distressing outcomes of dealing with MS. "To not go to work virtually every day and mix with other people on a day to day basis, has just knocked my for 6" It is clear that treatments are a factor in keeping people with MS in employment. The employment rate for people with primary progressive MS is 12% compare to 53% for relapsing MS.[6] Other research shows how much lower employment rates are for people with more severe MS - 37% for people with mild MS, and only 4% for people with severe MS.[7] Any treatments which delay the onset of more severe MS will have a positive impact on employment rates.

[4] MS Society (2017) *Employment that works: Supporting people with MS in the workplace* – APPG Report
[5] MS Society (2018) *Facing the future: Leaving work and MS*
[6] Data Source: Additional analysis of the MS Society, My MS My Needs Survey, a online and postal survey of 10,888 adults with MS in the U.K. Data was collected between February and April 2O16 by the MS Society. The final data set has been weighted to ensure it is representative of the MS Population, all analysis below excludes those who did not answer. Subgroup analysis of social care related to a sub sample who identified a social care need (n=6261). Full details of the survey are available at www.mssociety.org.uk.
[7] MS Society (2017) *Employment that works: Supporting people with MS in the workplace* – APPG Report

Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	Everyone we spoke to affected by secondary progressive MS echoed what we know about the current lack of effective disease modifying treatment, and the impact that has on their day-to-day life. One person reflected that current treatments "are far and few between, medication wise." Another summed up their care as "patchy" whilst another candidly referred to her care from the NHS as amounting to being told to "go away and get worse". [redacted] told us that her GP "didn't understand MS" and reflected lots of others when she said that services like the Continuing Care Team only seemed to work when prompted by patients. She talked about her MS nurse, which support disproportionately more people living with secondary progressive in large part due to the fact that there are no effective treatments. She said: "the MS Nurse is so busy it usually two or three days until they get back to me." On wheelchair services, Rosie highlighted long waiting times. "There is a 3 year waiting list to get a wheelchair. We went to a mobility place that had a second-hand one that was perfect. Otherwise, there was a three year waiting list". However, the local council services were referred to as a "lifeline". [redacted] said: ''I have a red button which is fantastic. If I have a fall, someone will come to the house in 20 minutes. That is an absolute boon. It's like getting a blue badge." Many people with secondary progressive MS, with no disease modifying therapies available to them, highlighted the poor symptom managed therapy options they currently have access to. Treatments for dealing with mobility are predominantly focused on exercise regimes and physiotherapy and it is important that people are able to access services to support this. Our research suggests that 45% of people with progressive forms of MS are currently accessing a physiotherapist.[8] Many people find that

[8] Data Source: Additional analysis of the MS Society, My MS My Needs Survey, an online and postal survey of 10,888 adults with MS in the U.K. Data was collected between February and April 2O16 by the MS Society. The final data set has been weighted to ensure it is representative of the MS Population, all analysis below excludes those who did not answer. Subgroup analysis of social

	fampridine significantly helps with their mobility but this treatment is not currently recommended as cost effective by NICE and is only available to those who are able to pay for a private prescription. Options for treating spasticity on the NHS include baclofen and gabapentin. While these and other treatments work for treating spasticity for some people with MS, our medical advisers have estimated that there is a sizeable portion of people with MS whose symptoms do not adequately respond to these options. They have suggested up to 10% of people with MS would be better treated with a cannabinoid based drug such as Sativex.[9] However this is another treatment which is currently recommended against by NICE for not being cost effective. [redacted], 59, living with secondary progressive MS told us: "Baclofen makes me very weak, which is quite counterproductive. I felt like a zombie. I tried three drugs and I didn't get on with them. I fell down the stairs backwards twice." [redacted] is now taking no licensed treatments for her pain and muscle stiffness and only taking one licensed other symptom management therapy, which was common among respondents. [redacted], living with secondary progressive MS told us: "I feel that pain relief is completely ignored. Anyone with MS will tell you they suffer pain. Pain relief is restricted constantly. GP's give the minimum to help. No-one should have to live in pain in this day and age, not when there is medication out there to help." [redacted], who is living with secondary progressive MS and is taking an off-label immunomodulatory treatment told us that the availability for treatments for progressive MS is "long overdue." She told us: "There are so many people like me. When you are in a situation where there is nothing [to treat SPMS], it's terrible. Once you're in my position in the UK, you don't qualify. In other countries people [with SPMS] stay on treatment a lot longer. It makes me really frustrated."

care related to a sub sample who identified a social care need (n=6261). Full details of the survey are available at www.mssociety.org.uk.

[9] MS Society (2017) *Cannabis and MS* [pdf] Available at: https://www.mssociety.org.uk/about-ms/treatments-and-therapies/cannabis/about-cannabis-and-ms

8. Is there an unmet need for patients with this condition?	**Estimated population** There are over 100,000 people living with MS in the UK. Approximately 40% of people with MS are not eligible for treatment that will slow or halt the progression of their disease.[10] People living with secondary progressive MS have a significant and persistent unmet need, which due the progressive nature of the condition, increases exponentially and disproportionally compared to people with other types of MS. 1 in 3 people with MS who need help with essential everyday activities like washing, dressing and eating aren't getting the support they need.[11] **Type of MS** A literature review by Pugliatti et al (2006)[12], recently updated, estimated that the proportion of people with the relapsing-remitting form of MS ranged between 31% - 55%. The MS Society uses the mid-point of the studies cited (43%), to provide a rough estimate the proportion of people with RRMS. We don't have an accurate estimate for people with primary progressive but from diagnosis rates we estimate that 15% of people with MS have primary progressive MS and approximately 42% live with secondary progressive MS. With new treatments less people living with relapsing-remitting MS are progressing to secondary progressive MS, so that figure is likely to decrease over time. Secondary progressive MS represents a huge unmet need in MS treatments. Currently there are 14 licensed disease modifying treatments for relapsing MS and one for primary progressive MS. People with secondary progressive MS have waited while licensed treatments for relapsing MS have increased and become more effective and easier to take. NICE should take into account the huge impact that this

[10] Disease Modifying Therapy (DMTs) in the UK among those who could benefit has increased from 40% in 2013 to 56% in 2016. Report. Available at: https://www.mssociety.org.uk/get-involved/campaign-with-us/treat-me-right/is-access-to-treatment-a-lottery
[11] MS Society (2017) https://www.mssociety.org.uk/what-we-do/news/1-in-3-people-with-ms-going-without-essential-care-and-support
[12] Pugliatti M, Rosati G, Carton H, Riise T et al. (2006) The epidemiology of multiple sclerosis in Europe. *European Journal of Neurology*; 13: 700-722

	treatment will have in reducing disability progression and offering people living with secondary progressive MS hope.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	[redacted], 59, living with secondary progressive MS, told us what having this treatment option could mean for her: "It seems like something I would try because the side-effects don't seem to be as onerous. If [my MS] would be slowed down that would be brilliant." The EXPAND trial was an international placebo-controlled, Phase 3 study of siponimod in a secondary progressive MS population. There were 77 patients based in the UK. Siponimod significantly reduced 3- and 6-month confirmed disability progression by 21% and 26%, as well as decline in cognitive processing speed and total brain volume loss versus placebo.
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	Siponimod being administered orally provides an easy to deliver treatment at a reduced long-term cost to the NHS through a lower impact on staff time. However, oral treatments do not offer a convenient treatment option for people that may have cognitive difficulties, for whom taking regular tablets and self-managing their treatment may be difficult, particularly if they lack support for administering treatment at home. [redacted] spoke for many when she told us "I cannot open the packets to pills so [redacted] [her partner] has to do that for it. It frightens me as to what would happen if I was on my own."
Patient population	

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Siponimod is going through the process of being licensed for "active" secondary progressive MS, which relates to the evidence of inflammation in the brain or spinal cord. People who do not perceive relapses but have worsening neurological disability do not have any treatment licensed to stop the progressive deterioration that can often have a neuroinflammatory component. People living with secondary progressive MS without relapses or evidence of inflammation have no such treatment and as such siponimod would not help them. MS can affect a person's ability to take oral medication which means siponimod will not be suitable for everyone, despite the restricted eligibility criteria.
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Many people with MS experience disability progression that significantly affects their mobility, often resulting in the need for mobility aids. The average person with MS will need to use a mobility aid within 20 years of diagnosis and a wheelchair within 30 years, though with treatment this prognosis is improving all the time. Women are three times more likely to be diagnosed with the MS, meaning that the range of disease modifying therapies available has a disproportionate impact on women. Women living with secondary progressive MS are highly likely to experience what the Lankelly Chase Foundation refer to as "multiple and severe disadvantage".[13] Due to the severe impacts and the complexity of the condition, increasing choice, and therefore access to treatment for MS, has a disproportionate impact on improving the life chances of people living with multiple and severe disadvantage.

[13]Corner and Duncan (2012) *Severe and Multiple Disadvantage: a review of key texts* [pdf] Available at: https://lankellychase.org.uk/resources/publications/severe-and-multiple-disadvantage-literature-review/

	The Equality and Human Rights Commission states that public authorities must take due regard to the impact of policies as relates to people's socio-economic status.[14] In the MS Society's' most recently national survey of over 10,000 people with MS (not yet published, to be kept confidential) 15% of respondents said they are "struggling" or "really struggling" on their current income. It found the people who were on any disability benefit were more likely to say they were struggling or really struggling on their current income. One person we spoke to as part of this appraisal highlighted this starkly, describing how they went into debt to have treatment that is routinely covered by the NHS, because of the significant delay to NHS treatment. They told us: "I had to borrow money from Zebra for the treatment [bladder Botox injections for spasticity]. I have used one of my credit cards and I am getting it on that."
Other issues	
13. Are there any other issues that you would like the committee to consider?	The majority of clinical trials for MS treatments have focused on relapsing MS, where people are diagnosed earlier and the effect of the treatment can be ascertained by the subsequent reduction of relapses, amongst other factors. Studying the effects of a drug on people with progressive forms of MS presents greater challenges. Those involved are likely to be at a higher EDSS score yet need to be assessed by the impact the treatment has on the disability progression alone. This means that longer trials are needed which take greater account of how upper limb function is impacted. When assessing the evidence NICE should consider that treatments for secondary progressive MS are currently an unmet need. Therefore if the evidence is not considered cost effective it is vital that an agreement is agreed which facilitates access to siponimod while more evidence is collected.

[14] Section 1(1) of the Equality Act 2010 provides that '[a]n authority to which this section applies must, when making decisions of a strategic nature about how to exercise its functions, have due regard to the desirability of exercising them in a way that is designed to reduce the inequalities of outcome which result from socio-economic disadvantage' referenced in Equalities and Human Rights Commission (2018) *Progress on Socio-economic rights in Great Britain*. Available at: https://www.equalityhumanrights.com/sites/default/files/progress-on-socio-economic-rights-in-great-britain.pdf

Key messages
15. In up to 5 bullet points, please summarise the key messages of your submission: • There is a significant unmet treatment need for people living with secondary progressive MS which siponimod would help to address. • Addressing this unmet need through ensuring equitable access to an effective treatment will benefit people experiencing multiple and severe disadvantage disproportionately. • The potential savings to the NHS and Social Services as a result of delaying disease progression, and the benefits to unpaid carers of people living with secondary progressive MS, are significant • The oral treatment option presents a cost effective option, but will not be suitable for everyone living with active secondary progressive MS, particularly if they experience cognitive problems. • The EXPAND trial clearly demonstrated the efficacy of this highly innovative treatment option

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

……

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

.....

NICE National Institute for Health and Care Excellence

Patient organisation submission

Siponimod for treating secondary progressive multiple sclerosis [ID1304]

Thank you for agreeing to give us your organisation's views on this technology 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.

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	Multiple Sclerosis Trust
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	The MS Trust is a UK charity dedicated to making life better for anyone affected by MS. The MS Trust is in contact with over 40,000 people affected by MS - that's people with MS, their families, friends and the health care professionals who help manage MS. Our core belief is that the best outcomes will come from well-informed people with MS making decisions in partnership with their specialist health professionals, and our aim is to support both sides of this partnership as much as we can. We provide expert information to help people with MS manage their own condition, and, uniquely, we inform and educate the health and social care professionals who work with them about best practice in MS treatment and care. We receive no government funding. We are not a membership organisation. We rely on donations, fundraising and gifts in wills to fund our services.
4b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	None.
5. How did you gather information about the experiences of patients and carers to include in your submission?	We have prepared this submission based on our experience of supporting people affected by MS at all stages of the condition. We speak daily to people who are dealing with issues relating to MS: coping with the impact of diagnosis, coping with physical, emotional and financial consequences of MS. To gain further insight into the views of those affected, we conducted an online survey of people with SPMS, their families and specialist MS health professionals, receiving 383 responses (29 August – 17 September 2019). 67% of survey respondents (n=257) stated that they have a confirmed diagnosis of SPMS, 14% (n=56) are relatives or friends of someone with SPMS. Their experiences provide a valuable

	personal perspective on living with SPMS, the impact it has on quality of life, and their perception of siponimod. Our response includes statistics and direct quotes from the survey. Working with people with secondary progressive MS (SPMS) and MS specialist health professionals, we have published a book which covers the physical and emotional aspects of living with SPMS and the ongoing management of the condition. The publication can be viewed on our website: Secondary progressive MS. Transitioning to SPMS is a significant milestone in the course of MS. Recognising the difficulties people often face when adjusting to their new diagnosis and the importance of supporting people reaching this stage, the MS Trust commissioned a team of researchers at Cardiff University to explore people's experiences of transitioning to SPMS from the perspective of patients, carers and clinicians[1,2].
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?	Most people with RRMS will eventually transition to a secondary progressive course in which there is a progressive worsening of neurologic function over time. It has been estimated that 10% of people with RRMS reach the SPMS stage after 5 years, which increases to 25% at 10 years and 75% at 30 years. As a progressive condition, SPMS has an impact on all aspects of life – physical, emotional, social and economic. These profoundly affect not only the person diagnosed with SPMS, but their families as well. **Diagnosis:** For most people with relapsing remitting MS (RRMS), transitioning to SPMS is a frightening and unwelcome milestone in the course of their MS. It represents the point at which current treatment with disease modifying drugs (DMDs) is withdrawn, contact with MS specialist health professionals is significantly reduced while increasing disability and loss of independence become major concerns. People often tell us that being diagnosed with SPMS is like being diagnosed with MS all over again, with

[1] Davies F, et al. 'You are just left to get on with it': qualitative study of patient and carer experiences of the transition to secondary progressive multiple sclerosis. BMJ Open 2015; 5(7): e007674.
[2] Davies F, et al. The transition to secondary progressive multiple sclerosis: an exploratory qualitative study of health professionals' experiences. Int J MS Care 2016; 18(5): 257-264.

all the same emotional reactions, uncertainties and worries for the future. Unfortunately, diagnosis of SPMS is often delivered in an unsupported way, with little explanation or information provided.

Significantly, nearly 22% (n=55) of people with SPMS responding to our survey reported that they had been diagnosed with SPMS from the outset, without a prior diagnosis of RRMS. We would acknowledge that this is self-reported and we have not been able to verify that respondents correctly interpreted the survey question. However, our experience of working with people with MS would confirm that a significant proportion of people are indeed diagnosed with SPMS from the outset, and can often recall early episodes of ill-health which in retrospect might have been signs of a relatively mild course of undiagnosed RRMS. It is vital that this group of people diagnosed with SPMS from the outset are not overlooked or excluded from potential treatment with siponimod.

- *I been symptom free for over 15 years whilst having Avonex weekly injections but when I was given the diagnosis of SPMS & Avonex withdrawn I was distraught and felt as if I had been given a death sentence.*
- *By the time I was diagnosed with ms it was clear that it had gone beyond the stage of rrms*
- *Had letter from neurologist informing me, was a shock and not best way to be told.*
- *I was ok with the diagnosis but disappointed to be discharged from a tertiary centre back to a general neurologist with no access to an ms nurse.*

Physical impact:

Transitioning to SPMS generally involves a worsening of pre-existing symptoms including mobility, fatigue, vision, bladder and bowel dysfunction and falls. Our survey asked people with SPMS how the condition affected them physically; out of 235 responses to this question, the symptoms most frequently selected were mobility problems (96%), balance and posture (92%) and fatigue (83%). Response to the full list of symptoms is shown below – this clearly shows the range of symptoms affecting people with SPMS:

- 96% Mobility problems
- 92% Balance and posture
- 83% Fatigue
- 80% Bladder or bowel problems
- 69% Spasticity and spasms
- 63% Pain and sensory problems
- 56% Cognitive problems

- 50% Sexual difficulties
- 50% Depression and anxiety
- 28% Vision and hearing
- 32% Speech and/or swallowing

People experience multiple symptoms; on average respondents selected 7 symptoms from the list.

Secondary symptoms arise as a consequence of the problems that MS brings. These may include falls due to walking or balance problems, muscle pain as a result of added strain on the back or legs caused by changes to gait, weight problems if there are mobility or swallowing issues, or the development of pressure sores due to lack of mobility. The effect of these symptoms is compounded, leading to increasing disability.

Survey respondents were asked to select their physical ability:

- 8% I can walk without help for at least 100 metres and largely look after myself
- 77% I need a stick, frame or wheelchair to get around and do need help with specific activities, but largely look after myself
- 16% I am dependent on a wheelchair or spend the majority of time in bed, and need a great deal of help with daily activities

- *My hands don't work very well.*
- *Symptoms are most acute when fatigued.*
- *I have had a colostomy because of bowel incontinence which also has its problems and has caused me to have sepsis twice in the last twelve months.*
- *I get throat spasms that make me feel like I can't breathe. I have oedema in my feet and lower legs.*
- *I need help to get washed and dressed every morning, I need help getting my meals prepared but still have the use of right arm, hand and leg*

Emotional impact:

SPMS can take a heavy psychological toll; in our survey, 84% of respondents (n=203) felt that SPMS had affected them emotionally.

Many respondents reported anxiety, depression, frustration, anger, isolation/abandonment and struggle to come to terms with increasing disability and loss of independence.

- *Much more sensitive, little confidence or self-esteem, unstable moods, intermittent suicidal feelings and ideation.*
- *There has been many a time I've wanted to sit and cry because I feel I'm too much of a burden to others and wanting to just give up.*
- *I suffer from anxiety and depression. I'm constantly stressed about the things I'm no longer able to do and am aware I can't really look after myself. I worry about how much more disabled I will come in the future and how I will cope.*
- *I'm miserable and drink alcohol so I can escape the pain and the reality of my life. I push people away and can't be honest with myself about how I feel let alone anyone else. If I keep saying I'm fine I try and think I'm fine.*

Others work hard to maintain a positive mental attitude, often with the support of partners:

- *Pseudo-bulbar affect is one of my symptoms. I am not depressed however and consider myself very fortunate to be lovingly and competently cared for by my dear husband.*
- *I used to be quite stressed but am laid back now. I haven't cried for years either.*
- *Feel angry and helpless, resulting in my having to follow a course in CBT- which helps me manage the above generally.*
- *Used to be suicidal, but have that under control now. Thanks to my partner.*
- *I was referred to neurology department by a physio helping me to recover from a knee operation. I went through stages of denial and feeling down before working things out with my family and working to make the best of things.*

Social impact:

In our survey, 86% of respondents (n=214) felt that SPMS had affected them socially. As SPMS progresses, people increasingly lose their independence and social activities require considerably more planning. Symptoms of SPMS, such as bladder and bowel incontinence can make activities particularly challenging; other aspects of SPMS can make people feel very self-conscious. Those who live on their own may not be able to go out alone and social isolation becomes a major concern.

- *As a member of an amateur dramatic society I have had to give up, acting and backstage work. I now only do support and administrative duties but these are becoming harder due to fatigue and cognitive process becoming a problem as we meet in the evenings when these symptoms are at their worst. This is also upsetting.*
- *Fatigue and can only go where there is disabled access and toilets .I have missed family weddings, baptisms, funerals including my fathers.*
- *I struggle to keep up in conversation and in a group. I don't get involved in as many activities as I'd like due to mobility and fatigue ie WI.*
- *Can't go out for meal as embarrassing to choke for no reason drop things with hand tremors danger of falling in low lights*

- *Can no longer be spontaneous, everything now is like a military operation - going out, going on holiday, going shopping, the hairdresser..... Every day is hard work.*

Economic impact:

Although NICE cost effectiveness calculations do not take account of the burden of loss of work, remaining in work is of critical importance to people with SPMS, not only for economic reasons but also for maintaining social contact, self-confidence and a sense of purpose. Survey respondents frequently mentioned their efforts to continue in paid employment (sometimes at the expense of other activities) or expressed regret at the loss of a working life and economic independence. Some who continue to work have had to change their role and recognise that MS has limited their opportunities for career progression. Out of the 235 survey respondents, just 7% were in paid employment, a further 8% had had to reduce working hours since diagnosis, and 46% reported that they had stopped work early or were unable to work due to ill health. A treatment which delays progression has potential to help people with SPMS stay in work for longer, benefiting the individuals concerned as well as benefiting the wider economy.

The impact on work of the different types of MS have not been studied in the UK population but results from Scandinavian studies might be expected to apply to the UK. A Norwegian study conducted[3] in 2014 reported that just 24.3% of people with SPMS were employed full or part-time, compared with 66.1% with RRMS and 14.8% with primary progressive MS. Similarly, a Swedish study[4] reported that people with SPMS had significantly lower income than people with RRMS.

- *I've had to give up my career of 10 years as a Paramedic, which I adored. I am fighting to stay at work, in an alternative role, but without treatment my working life will, undoubtedly, soon be coming to an end, which will completely crush me.*
- *I continue to work full time but have had to change my role and have moved out of the typical progression due to my MS.*
- *Had gradually reduced my hours over the past couple of years, but having had more time off sick in the last year than I had in the previous 5 years, I reluctantly finished work a few weeks ago.*
- *I finally, but reluctantly, had to give up work as I could no longer function well enough to continue. This has upset me a great deal.*

Caregiver impact:

[3] Boe Lunde HM et al. Employment among patients with multiple sclerosis – a population study. PLoS One 2014; 9(7): e103317.
[4] Kavaliunas A et al. Income in Multiple Sclerosis Patients with Different Disease Phenotypes. PLoS One. 2017;12(1): e0169460.

	SPMS does not only impact the individual, but also family and friends who may provide formal/informal care. With increasing disability, people with SPMS become more and more dependent on carers for their personal care and to access activities outside the home. This can strain relationships, as family members may need to take on additional responsibilities. Caregiving partners may feel uncertainty about the future, financial difficulties, social disruption and isolation. • *I have witnessed the devastating effects of SPMS first hand. It has torn my family apart*.[respondent's daughter died from aspiration pneumonitis secondary to SPMS] • *Having watched my father go from being mobile to being in a care home in his 50s was heart breaking. He couldn't even make it to my wedding. He would have jumped at the chance to slow down it progression.* • *I am a single, widowed mother with SPMS - just 5 years ago I didn't know I had MS and now I am reliant on a wheelchair. My son is* [redacted]*. The progression of my MS has not only resulted in my care needs increasing but also meant my son has required additional intervention and support.* • *My family have had to watch a vibrant, fit woman, mother, grandmother become a shadow of herself, slowly becoming trapped in a non functional body.* • *Such hard work for my wife of 47 years who retired from her work to be my sole carer once I became wheelchair dependent in 2003.*
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	Management of SPMS focuses on four key areas: symptom management; prevention of complications; maintaining function and promoting general health and wellbeing. Given the wide range of symptoms that people with SPMS may experience, it is important that there is access to a range of therapies delivered by skilled allied health professionals, competent in MS care. In reality, access to NHS and social care interventions to support people living with SPMS such as physiotherapy or neurorehabilitation are limited, sporadic or even non-existent in some places. The quality of and access to care is highly dependent on where someone lives. Calculation of the cost of providing 'established clinical management' cannot assume an ideal situation where these services are readily available. Our survey asked people with SPMS about contact with MS specialist health professionals in the last 12 months. • 64% had seen a neurologist

	• 69% had seen an MS nurse • 8% had seen neither, but would have liked to • 1.7% had seen neither, but by choice Comments on this question noted how difficult it was to see a neurologist since being diagnosed with SPMS. Waiting times to see a neurologist can be very long, one respondent stated more than two years. • *I used to see the neuro every year. Since being told I have SPMS I'm told I can only see the neuro if I need to. I have no follow up appointment.* • *I was essentially discharged by the neurologist as he stated there wasn't really anything he could do.* • *Told I'm SP now so won't see neurologist any more.* These comments are supported by a survey[5] conducted by the MS Trust in 2016 which found that, on average, people with progressive MS are seeing MS specialists much less often than people with RRMS. Furthermore, 40% of people with SPMS reported seeing less of their specialists once their disease became progressive. Many reported being effectively 'discharged' from the care of their neurologist and their MS specialist nurse and left to manage alone, with increasing disability and more complex symptoms. Our survey respondents also reported how often they had used other NHS services; those most frequently accessed include: • 67% Family doctor • 43% Physiotherapist • 32% Continence advisor • 26% Occupational therapist • 21% A&E • 19% Chiropodist • 17% Other specialist nurse • 15% Community/district nurse • 9% Orthotist

[5] MS Trust. Is MS care fair? MS Trust; 2016

	• 8% Rehabilitation medicine team A number commented that access to care, particularly physiotherapy, was inadequate or they had to pay for private treatment. • *Privately see physio twice a month....unavailable on NHS.* • *Have been awaiting to see a Continence advisor for the past eight months.* • *I pay privately for my feet to be done* Survey data collected by the MS Trust shows that MS neurologists and MS nurses also identify many of these therapy services as patchy or insufficient in their area[6]. 'Established clinical management' is not defined in the final scope, but it is clear from the data collected in our survey that people with SPMS have a high level of need for NHS care that is currently not being provided. There is currently no research or professional consensus on what 'established clinical management' is or how much it costs; any definition will be idealistic. It is unrealistic to assume that all people with MS have access to high quality care that fully meets their needs. The reality is that people with MS often have very limited access to services. The quality of and access to care is highly dependent on where an individual lives. In practice, because there are no treatments for secondary progressive MS, clinicians delay diagnosis and continue to prescribe disease modifying drugs beyond the transition from RRMS to SPMS. For an accurate picture of the current cost to the NHS of treating SPMS, this appraisal should acknowledge that disease modifying drugs continue to be used at least up until an established EDSS 7, even though this use is not strictly covered by licensing. We note that, in the final scope, interferon beta 1b (Extavia) is included as a comparator. We do not believe that interferon beta 1b should be considered as a comparator; it reduces the number and severity of relapses and is licensed for patients with secondary progressive multiple sclerosis with relapses (active disease). In contrast, siponimod reduces confirmed disability progression independent of an effect on

[6] MS Trust. Improving services for people with advanced MS. MS Trust; 2016

	relapses (non-active disease)[7]. Furthermore, the committee will be aware that in England the prescribing of interferon beta 1b (Extavia) is very low, especially in people with secondary progressive MS with relapses. Low use of Extavia is largely due to difficulties with taking it. Extavia is supplied as solvent and powder which must be made up each time it is taken. The Patient Information Leaflet[8] for Extavia details the seventeen step instructions for doing this. People with manual dexterity, visual or cognitive difficulties, all of which are common problems in SPMS, will find this very difficult, if not impossible, to do.
8. Is there an unmet need for patients with this condition?	Time and again respondents to our survey commented that there is currently no treatment to delay the progression of SPMS, nothing that can change the prognosis of their condition. Many people are doing all that they can to minimise the impact of SPMS, but they are all too aware that there is nothing that will slow down the progression of their disease. • *So now it feels like I've got nothing to look forward to but things continuing to get worse, and with no DMT treatments currently available for SPMS, there's no hope of ever being able to stop, or even slow down, further deterioration. So this is it... downhill all the way to the end!* • *My sister has been very brave facing this awful life changing illness although mentally and emotionally it has been exhausting for her. She knows there is no cure but any medication and research that could go into easing the symptoms and slow the progression down would make her difficult life easier.* • *I see my partner slowly becoming more disabled. Over the last few years she has lost use of her legs and left arm, for us it is a daily fight to save the reducing ability of her right arm to keep her independent. Any drug that can delay this process has to be an option for NHS prescription.* In the absence of a cure, the biggest unmet need for people with SPMS is a treatment which can slow down or stop progression of disability in SPMS. In the absence of a treatment to slow down SPMS, the biggest unmet need remains access to the full range of NHS services on demand and coordination of services to ensure rapid referrals at times of critical need. From our experience, capacity for this is not currently available.

[7] Cree B, et al. Uncoupling the impact on relapses and disability progression; siponimod in relapsing and non-relapsing patients with secondary progressive multiple sclerosis in the phase III EXPAND study. Neurology 2018;90(15 Supplement):S8.005.
[8] Extavia Patient Information Leaflet.

Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	The clinical trial data have demonstrated the effectiveness of siponimod at delaying progression in SPMS. Fewer people taking siponimod had an increase in disability, compared to placebo. An increase in disability which lasted 12 weeks was seen in 26% of those taking siponimod and 32% of those taking placebo (relative risk reduction 21%)[9]. Subgroup analysis indicated a 33% relative risk reduction for those with "active" SPMS (defined as those who had relapsed in the two years prior to starting the trial)[10]. Siponimod was also more effective than placebo on other measures used in the study: • reduced risk of 6 month confirmed increase in disability • reduced loss of brain volume • reduced MRI-detected brain lesion volume • improved cognition through an improvement in information processing speed The overwhelming majority of respondents to our survey (99%, n=321) are delighted that there is, at last, potential to slow down the progression of their condition; over the years as the number of treatments available for RRMS have grown, people with progressive MS have felt that their needs have been forgotten. Many respondents to our survey recognised that their SPMS may be too advanced to gain a benefit, but believed others should be given the opportunity to take a medication that would slow down progression. The benefits of slowing down progression are seen as maintaining mobility and independence for longer, allowing people to continue to work for longer, and saving costs for the NHS in the long term by preventing progression and the need for MS services and social care. Several respondents hoped that siponimod would kick start development of other treatments for secondary progressive MS:

[9] Kappos L, et al. Siponimod versus placebo in secondary progressive multiple sclerosis (EXPAND): a double-blind, randomised, phase 3 study. Lancet 2018; 31;391(10127):1263-1273.
[10] Gold R, et al. Efficacy of siponimod in secondary progressive multiple sclerosis patients with active disease: the EXPAND study subgroup analysis. Mult. Scler. 2019, 25:2_suppl, 357-580, P750.

	• *It would be the first treatment available for SPMS, and hopefully will be the start of other treatments so we won't feel ignored.* • *This could kick start development of other meds for SPMS.*
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	Very few people expressed reservations about siponimod. A small number (5%, n=18) expressed concern about potential side effects and would want to have an informed discussion about benefits and risks before making a decision. Expectations of treatment will need to be managed; people will need to be counselled that siponimod will not necessarily make them better, but will slow down the rate at which they get worse. Undoubtedly, there will be disappointment when some people learn that they are not eligible for siponimod. Experience gained from MS teams in the United States and other countries where siponimod is approved will be invaluable to manage expectations and identify potential risks.
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so,	The wording of the licensed indication may specify subgroups of patients with secondary progressive MS most likely to benefit from siponimod treatment. As noted in the response to question 6, our survey identified a significant proportion of respondents (22%, n=55) who considered that they had been diagnosed with SPMS from the outset. It is vital that this group of people diagnosed with SPMS from the outset are not overlooked or excluded from potential treatment with siponimod.

please describe them and explain why.	
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	None.
Other issues	
13. Are there any other issues that you would like the committee to consider?	Siponimod is taken orally once daily at home, a route of administration which is generally preferred by patients, leads to good adherence and has low impact on NHS services. It is also anticipated that monitoring requirements (for example blood and urine tests) for siponimod will be moderate with low impact on NHS services. However, we recognise that MS services are likely to be overstretched by demand for the first treatment for SPMS; at the earliest opportunity it will be important to communicate eligibility criteria and manage expectations. MS services will also need to consider reinstating contact with patients who have been discharged from neurological services.

	The introduction of disease modifying drugs for RRMS has been the catalyst for significant improvements in MS services for people with relapsing MS. The introduction of a treatment for SPMS would similarly result in a greater focus on services for progressive MS and a more pro-active approach to managing the condition which would ultimately benefit a much wider group of people with SPMS than just those who might be eligible for siponimod.

Key messages

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

- Secondary progressive MS is a challenging milestone, characterised by increasing disability and loss of independence
- Increasing disability has an impact on physical and emotional well-being for the individual and family members who act as informal carers, causing anxiety, depression and leading to breakdown in relationships
- SPMS has significant social and economic impact as people are less able to work and contribute to society in a way that has meaning for them
- Current management of SPMS is inconsistent as access to appropriate therapies is difficult or only available through private healthcare, which is not an option for those unable to work or on low incomes
- Siponimod is the first treatment which has been shown to slow down progression in SPMS, which in turn improves health outcomes and thus alleviates the impact of SPMS.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

.....

Your privacy

NICE National Institute for Health and Care Excellence

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

……

NICE National Institute for Health and Care Excellence

Professional organisation submission

Siponimod for treating secondary progressive multiple sclerosis [ID1304]

Thank you for agreeing to give us your organisation's views on this technology 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.

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 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**Association of British Neurologists**

3. Job title or position	[redacted] [redacted]
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 this condition? ☒ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	**The Association of British Neurologists is the professional society for neurologists and clinical neurology researchers in the United Kingdom; it has 1250 members. The aim of the Association of British Neurologists is to promote excellent standards of care and champion high-quality education and world-class research in neurology. It is funded by member subscription.**
5b. 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	To reduce cumulative disability progression (CDP) in patients with secondary progressive multiple sclerosis (MS)

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 reduction of CDP by 20%. This treatment reduces CDP by 21% at 3 months and 26% at 6 months.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes, a great unmet need - there is currently no treatment for this group of patients
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	Supportive management only.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	NICE Guidance CG186 As this is the first treatment there is no guidance available to alter the course of secondary progressive MS

• 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.)	Well defined. No real difference of opinion.
• What impact would the technology have on the current pathway of care?	A significant impact as treating an unmet need. It would result in a large increase in patient numbers. However, being an oral therapy, it should be fairly seamless aside from initial cardiac monitoring in a select group.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	It will be used in a similar way as treatments for relapsing and remitting MS but for those with evidence of ongoing disease progression.
• How does healthcare resource use differ between the technology and current care?	Similar to one of the existing drugs fingolimod which is used for relapsing and remitting MS - initial cardiac monitoring, 3 month ophthalmology check, ongoing blood test monitoring.
• In what clinical setting should the technology be used? (For example, primary or secondary	Specialist clinics

care, specialist clinics.)	
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Increase in clinic capacity. No significant facilities or training requirement
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes, it represents the first ever treatment to reduce CDP in secondary progressive MS with add-on reduction in requirements for symptomatic therapies, supportive care, prolonged ambulation, increased time in employment etc.
• Do you expect the technology to increase length of life more than current care?	Yes, it has been shown to extend ambulation time and delay onset of permanent wheel chair use.
• Do you expect the technology to increase health-related quality of life more than current care?	Definitely – there is currently only symptomatic support.
12. Are there any groups of people for whom the technology would be more or	The current data does not indicate a more responsive sub group (ie MRI activity - the study was not powered to do so).

less effective (or appropriate) than the general population?	
The use of the technology	
13. 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.)	Current care is supportive. It is a daily oral treatment which is well tolerated. It may cause bradycardia, a subgroup will require 6 hours of ECG monitoring as well as an ophthalmology review at 3 months for rare macular oedema – this is already in place in all MS treatment centres
14. Will any rules (informal or formal) be used to start or stop treatment with the technology?	It will be used in patients with secondary progressive MS and evidence of ongoing progression – no additional testing required.

Do these include any additional testing?	
15. 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?	Reduced demand for relatives to leave their employment in order to become carers.
16. 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?	Yes, by reducing the accumulation of neurological disability.
• Is the technology a 'step-change' in the management of the	It is the first treatment to reduce

condition?	
• Does the use of the technology address any particular unmet need of the patient population?	Partially – it is not a cure.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Not significantly. Initial ECG monitoring, ophthalmology review and then blood test surveillance.
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes
• If not, how could the results be extrapolated to the UK setting?	N/A
• What, in your view, are the most important outcomes, and were they	They utilised the most important outcomes:- CDP at 3 and 6 months, MRI markers including T2 lesions, Gd enhancement and brain volume.

measured in the trials?	
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	N/A
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No
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 [TAXXX]?	No significant published data. Further supportive information presented at recent ECTRiMS meeting.

21. How do data on real-world experience compare with the trial data?	The rate of progression seems in keeping with RWE.
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
22b. Consider whether these issues are different from issues with current care and why.	No
Key messages	

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

- First drug to reduce disability in secondary progressive MS
- Improvement in all MRI indices
- Well tolerated
- Ease of Use
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

……

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

……

NICE National Institute for Health and Care Excellence

Professional organisation submission

Siponimod for treating secondary progressive multiple sclerosis [ID1304]

Thank you for agreeing to give us your organisation's views on this technology 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.

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 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**UKMSSNA**

3. Job title or position	**UKMSSNA**
4. Are you (please tick all that apply):	**x** an employee or representative of a healthcare professional organisation that represents clinicians? ☐ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	**Represents MS Specialist Nurses from the 4 Countries. Funding from members.**
5b. 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	To decrease the risk of disability and relapses

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.)	Reduction in the rate of disability
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Limited treatments available within the progressive forms of MS
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	Limited treatments available so would give clinicians additional options
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	MS Guidance

• 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.)	Defined but will always have some subjectivity due to the unpredictability of MS
• What impact would the technology have on the current pathway of care?	Enhance options
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	New treatment
• 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	Secondary and specialist clinics in either settings

care, specialist clinics.)	
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Training, additional clinic time, further clinical tests and additional clinical/nurse/doctor time
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes
• Do you expect the technology to increase length of life more than current care?	Possibly
• Do you expect the technology to increase health-related quality of life more than current care?	Yes
12. Are there any groups of people for whom the technology would be more or	Unknown

less effective (or appropriate) than the general population?	
The use of the technology	
13. 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.)	Additional treatment option
14. Will any rules (informal or formal) be used to start or stop treatment with the technology?	Guidance will be needed on this

Do these include any additional testing?	
15. 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?	
16. 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?	Yes
• Is the technology a 'step-change' in the management of the	Yes in some instances

condition?	
• Does the use of the technology address any particular unmet need of the patient population?	Yes
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	
• 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?	
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 [TAXXX]?	No

21. How do data on real-world experience compare with the trial data?	
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
22b. Consider whether these issues are different from issues with current care and why.	
Key messages	

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

-
-
-
-
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

……

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

x **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

……

NICE National Institute for Health and Care Excellence

Clinical expert statement

Siponimod for treating secondary progressive multiple sclerosis [ID1304]

Thank you for agreeing to give us your views on this technology 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.

Information on completing this expert statement

- 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 13 pages.

About you	
1. Your name	**Carmel Wilkinson**
2. Name of organisation	**South Tyneside and Sunderland Foundation Trust, representing the UKMSSNA**

3. Job title or position	
4. Are you (please tick all that apply):	☐ **x** an employee or representative of a healthcare professional organisation that represents clinicians? ☐ **x** a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition 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)	☐**x** yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't 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.)	☐**x** yes

The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To reduce risk of disability and relapse of MS
8. 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.)	Reduced rate of disability
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Limited therapy option for progressive disease – first of its kind -
What is the expected place of the technology in current practice?	

10. How is the condition currently treated in the NHS?	Restricted options for secondary progressive
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	NICE MS clinical guidelines ABN algorithm
• 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.)	In places yes, there is always a degree of clinical judgement which requires experience and subjectivity in the varying presentations of MS. There will always be differences of clinical opinion based on experience, but there will always be consensus available.
• What impact would the technology have on the current pathway of care?	Improve options in the evolving disease
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	This is a new treatment

• How does healthcare resource use differ between the technology and current care?	This will be used across two settings – acute neurology and rehab within specialist centres.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Prescribing centres – secondary care
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Education and training Clinical testing Impact on neurologist/specialist clinic time
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes, hopefully
• Do you expect the technology to increase length of life more than current care?	Uncertain, but potentially yes
• Do you expect the	Yes

technology to increase health-related quality of life more than current care?	
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Secondary progressive phase of MS
The use of the technology	
14. 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	Additional to current care. Additional clinical requirements – monitoring burden currently not in place

or ease of use or additional tests or monitoring needed.)	
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Clear eligibility and cessation criteria must be set
16. 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?	yes
17. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related	Yes

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?	Yes – currently limited options
• Does the use of the technology address any particular unmet need of the patient population?	yes
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Uncertain as yet. Hospital attendance and monitoring burden may impact
Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	yes

• 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?	Reduction in speed of progression, predicted reduction of continued disease progression
• 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?	Unsure re the significance of S/E's long term
20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	no
21. Are you aware of any new evidence for the comparator	No

treatment(s) ?	
22. How do data on real-world experience compare with the trial data?	
Equality	
23a. Are there any potential equality issues that should be taken into account when considering this treatment?	no
23b. Consider whether these issues are different from issues with current care and why.	n/a
Key messages	

25. In up to 5 bullet points, please summarise the key messages of your statement.

- Current unmet need in progressive disease
- Additional treatment option for a significant cohort of MS patients
- Full eligibility and stopping criteria required
- consensus on stopping criteria required
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

……

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ x**Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

……

NICE National Institute for Health and Care Excellence

Patient expert statement

Siponimod for treating secondary progressive multiple sclerosis [ID1304]

Thank you for agreeing to give us your views on this technology 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.

Information on completing this expert statement

- 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	**Jacqueline Krarup**
2. Are you (please tick all that apply):	☒ a patient with the condition? ☐ a carer of a patient with the condition? ☐ a patient organisation employee or volunteer?

	☐ other (please specify):
3. Name of your nominating organisation	MS Society Registered charity 1139257; Company limited by guarantee 07451571
4. Did your nominating organisation submit a submission?	☒ yes, they did ☐ no, they didn't ☐ I don't know
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 didn't submit one, I don't know if they submitted one etc.) **Please check the box that suits.**

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.)	☐
7. How did you gather the information included in your statement? (please tick all that apply)	☒ I have personal experience of the condition ☐ I have personal experience of the technology being appraised ☐ I have other relevant personal experience. Please specify what other experience: ☐ I am drawing on others' experiences. Please specify how this information was gathered:
Living with the condition	
8. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	As a patient with secondary progressive MS (PwSPMS) living with the condition is relentless, often painful and exhausting. There is currently no treatment, so life is unpredictable and I fear what the future will hold. My mobility is very restricted, my vision blighted by optic neuritis, bowel and bladder control is severely compromised and I regularly experience excruciating pain from trigeminal neuralgia, a nerve pain that send shocks from the brain down the right side of my face. I cannot walk unaided, never without a walking stick, for more than 5-10 metres before stopping. I must always have something fixed to grab at short regular intervals in order to prevent a fall. I can still drive an automatic vehicle but can rarely go to new places as it is difficult to comprehend new routes, unfamiliar surroundings and I always must plan where to park (even though I have a disabled 'blue badge'). On top of this I need access to a loo the moment I arrive or leave anywhere in order to avoid embarrassing circumstances. I am therefore fearful of going out alone.

	I no longer work, in regular paid employment, as it is stressful and difficult to absorb, learn and comprehend new information, let alone get to a place of work. I need regular rests to overcome my constant fatigue. It is frustrating because as my symptoms gnaw away and gradually worsen there is no medical treatment I can take to stop the deterioration. I know that in perhaps less than a year I will have to rely on a wheelchair whenever I leave the house. Living in rural countryside this will not be easy. Outside and inside the house I always use my stick and grab rails have been inserted in critical places including the bathroom and kitchen. My husband is forever supportive but is frustrated knowing that nothing is being done to 'fix the problem'. He works long hours away from home and we both know this is unsustainable in the long run. If he were to retire early, we would have to adjust our lifestyle. My two adult children live independently and work away from home but again they are anxious about my safety, especially as I am at home alone for much of the day, and what will happen as my condition worsens and I can no longer get about at all.
Current treatment of the condition in the NHS	
9. What do patients or carers think of current treatments and care available on the NHS?	As a patient, overall the care I receive on the NHS is patchy to good. The good part is entirely due to the understanding nature and care provided by the MS nurses. They will always respond within 24 hours to the helpline and will never refuse an appointment however stretched they are. The patchy part relates to the appointments with the neurologist which are restricted to once a year and recent experience has been frustrating. At the last appointment **12 months ago,** I was left to say what I think I need and he as good as said there is nothing that can be done and dismissed me by signing the form to book another appointment in a year's time. This appointment has just been changed and extended by the NHS by a further 2 months. Over 14 months since the last appointment with a neurologist at my local hospital is unacceptable. Frankly, I would rather contact the nurses for help. I do have the benefit of having been on the MS-STAT2 drug trial (for Simvastatin) at UCLH so have access to the neurologists there who have been helpful. Whilst this may work for myself and in a few isolated cases, other patients with SPMS who are registered at Northampton NHS Trust may not have such access to alternative care and I have concerns for them. I have evidence of this anecdotally from the other patients with SPMS in my local MS Northamptonshire Group. Treatments for the earlier stage of the condition, RRMS, are encouraging given that there are now 14,

	perhaps 15, licensed disease modifying treatments (DMTs). The earlier a diagnosis can be given the better and more effective the DMT can be. For patients with PPMS (primary progressive MS) there is now one drug treatment available, ocrelizumab, with several in the pipeline (and thankfully this is the focus of the STOP MS Appeal). It is however the patients with SPMS that are left in limbo struggling to piece together a care package which typically consists of an exercise programme/physiotherapy (which can't always be provided at the patient's home, so access is difficult) and treatments for temporary pain relief. Taking ad hoc pain relief medications is becoming more frequent – firefighting rather than trying to address the root cause – although this can have implications, not just on budgets in terms of having to prescribe more drugs, but more importantly on overall health of patient with SPMS - especially when taking part in a drug trial (I can speak from personal experience here). I talk about the lack of treatments, not just personally, but also for other patients with SPMS with whom I am in regular contact with. Ad hoc medications to treat symptoms of SPMS is not, I strongly believe, the definitive answer.
10. Is there an unmet need for patients with this condition?	For patients with SPMS, absolutely. There are currently no licensed medications to treat SPMS. Sativex is effective for treating certain symptoms including muscle spasms, as is Baclofen and other drugs are prescribed to treat various symptoms such as, for example, carbamazepine to treat severe pain associated with trigeminal neuralgia. These drugs treat symptoms rather than stop the damage being caused by immune attacks on the nerve cells in the brain and spinal cord. With no effective treatment to address the root cause, patients with SPMS will continue to experience worsening symptoms which in the long run will present a hefty burden on the NHS and care support budgets.
Advantages of the technology	
11. What do patients or carers think are the advantages of the technology?	The treatment drug will be taken orally thus convenient for the patient and simple to administer for both patient and clinician. The advantages will be huge in terms of slow down/elimination of disability progression. The drug needs to be available for all patients with SPMS for whom there is currently no treatment. The side effects are minimal; the health and economic benefit in the long run would, I envisage, outweigh the costs. This must be a win-win situation. Ultimately, I would like to see a world where there is no SPMS because diagnosis and treatment of RRMS can be made and treatments administered early in the course of the progression of the condition.

Disadvantages of the technology	
12. What do patients or carers think are the disadvantages of the technology?	I can envisage a disadvantage whereby patients with SPMS, especially those experiencing 'cognitive fog' may forget to take the drug. As with other medications I am sure this can be overcome with a simple and inexpensive pill dispenser box which labels the days, like the tablet box used by patients with Alzheimer's. It is perhaps important that a career/family member helps with the drug administration.
Patient population	
13. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	It is hoped that all patients with SPMS who are eligible (i.e. have evidence of active inflammation in the brain or spinal cord) will have immediate access to the drug. I think I am correct in understanding, however, that in as many as 2/3 of patients with SPMS show no new evidence of inflammation which can be seen on the MRI scan, despite worsening symptoms, so Siponimod might not be as suitable for or help them? Notwithstanding, this should not underline its importance for those patients with 'active' SPMS where inflammation is prevalent.
Equality	
14. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	It is important that the drug licensing must be backed by a proportionate marketing budget to make all patients with SPMS and their families/carers, who are eligible, aware of its availability on the NHS and support given to those patients who are struggling with affordability (even on the NHS).

Other issues	
15. Are there any other issues that you would like the committee to consider?	Siponimod isl only likely to be effective for those patients with SPMS who are showing evidence of inflammation on the brain and spinal cord. I understand that up to 2/3 patients show no evidence of (new) inflammation on the brain, despite experiencing worsening symptoms, so Siponimod might not be suitable for them. Notwithstanding given that currently there are no treatments for SPMS, this drug meets an unmet need and licensing would benefit a good number of patients suffering from SPMS. Notwithstanding any debates on its cost effectiveness, given that there is currently no other drug available, or close to submission, access to Siponimod for patients with SPMS should be approved.

16. In up to 5 bullet points, please summarise the key messages of your statement:

- There is currently no licensed drug treatment for patients with SPMS.
- Taken orally, the drug is easy to administer by clinicians and for patients with SPMS.
- In the long-term cost savings will be made by the NHS and Social Services as SPMS
- Its cost effectiveness may require more analysis, this should not hold up access to the drug for patients with SPMS in the short term.
- Doing nothing/withdrawing consent will result in more ad hoc treatments being given to patients with SPMS that address symptoms only. In the long run this would prove both more expensive and detrimental to the overall health and wellbeing of the patient.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

.....

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

.....

NICE National Institute for Health and Care Excellence

Patient expert statement

Siponimod for treating secondary progressive multiple sclerosis [ID1304]

Thank you for agreeing to give us your views on this technology 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.

Information on completing this expert statement

- 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	**Caroline Smith**
2. Are you (please tick all that apply):	☐ √ a patient with the condition? ☐ a carer of a patient with the condition? ☐ a patient organisation employee or volunteer?

	☐ other (please specify):
3. Name of your nominating organisation	The MS Trust
4. Did your nominating organisation submit a submission?	☐ √ yes, they did ☐ no, they didn't ☐ I don't know
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 didn't submit one, I don't 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. How did you gather the information included in your statement? (please tick all that apply)	☐ √ I have personal experience of the condition ☐ I have personal experience of the technology being appraised ☐ I have other relevant personal experience. Please specify what other experience: ☐ I am drawing on others' experiences. Please specify how this information was gathered:
Living with the condition	
8. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	MS effects every part of life, symptoms are so wide-ranging and unique to the individual. We all have different experiences of MS which means there is a lack of understanding and support within the community but also the medical profession, when asking for help we have to become educators as the people we are asking don't get it and so cannot help. Transitioning to SPMS was traumatic as I knew no treatment was available and I was no longer able to attend a specialist MS clinic. MS has stopped me working, causes pain, fatigue, unsteadiness, dizziness, bladder problems, anxiety and depression as well as cognition issues. I am unsafe in the kitchen and need a lot of support with everyday living. I am facing a life of increasing disability with no treatment options, and often quite poor symptom control. My life expectancy is not very different to the norm so I will probably live for over half my life with SPMS

Current treatment of the condition in the NHS	
9. What do patients or carers think of current treatments and care available on the NHS?	All I have available to me is symptom control, there is no treatment for SPMS. There is limited care from the NHS, I cannot see an MS specialist neurologist as I am SP and can only see an MS nurse once a year which I am grateful for as MS nurses are overworked and have to prioritise seeing those with RRMS who are on treatment. I struggle to know what specialist services are available and so cannot see the most appropriate physios and other health professionals which again wastes time as they do not have enough knowledge of MS
10. Is there an unmet need for patients with this condition?	Yes. There is no treatment for SPMS and current services prioritise those with RRMS who are on treatment. Many people with SPMS are solely managed by their GPs rather than specialists
Advantages of the technology	
11. What do patients or carers think are the advantages of the technology?	It is the first treatment aimed at those with SP MS and gives hope of slowing progression as well as keeping people involved with specialist services
Disadvantages of the technology	
12. What do patients or carers think are the disadvantages of the technology?	It will not be suitable for all with SPMS so many will continue to be frustrated by a lack of treatment
Patient population	
13. Are there any groups of patients who might benefit	There are many people with SPMS who are not under consultant neurologists and will not have access to this treatment. MS neurologists and nurses are already under great pressure and lack the clinic

more or less from the technology than others? If so, please describe them and explain why.	capacity to take on many more patients so will not be able to support all patients with MS adequately, There is no register of people with MS so some who may benefit will not be made aware of it as an option
Equality	
14. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	**There are currently very big differences as to the treatment and levels of care provided to those with progressive MS as opposed to those with relapsing disease. This technology could help reduce these inequalities**
Other issues	
15. Are there any other issues that you would like the committee to consider?	We are unsure of total numbers of people with MS and the exact numbers with SPMS, but surveys indicate that the split between RRMS and progressive forms is approximately 50:50 so there is potentially big benefits to slowing disease progression in SPMS

16. In up to 5 bullet points, please summarise the key messages of your statement:

- People with SPMS are currently treated very differently to those with progressive disease
- SPMS effects all parts of a persons life, symptoms are many and varied but there is no treatment
- It is estimated that 50% of people with MS have progressive forms

- Current provision of MS Neurologists and MS nurses will struggle to deal with additional treatment options for a group of patients that currently are not seen in clinics
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

.....

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

.....

NICE National Institute for Health and Care Excellence

Clinical expert statement

Siponimod for treating secondary progressive multiple sclerosis [ID1304]

Thank you for agreeing to give us your views on this technology 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.

Information on completing this expert statement

- 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 13 pages.

About you	
1. Your name	**Dr Matt J Craner**
2. Name of organisation	**Frimley Health Foundation and University of Oxford**

3. Job title or position	**Consultant Neurologist and Clinical Director MS trials Unit**
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 this condition? ☐ a specialist in the clinical evidence base for this condition 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 didn't submit one, I don't 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

The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Most people with Relapsing Remitting Multiple Sclerosis (RRMS) will over time develop secondary progressive MS (SPMS). It is noteworthy, that although literature often describes two natural history phases of the disease (RRMS and SPMS) they represent a spectrum that transitions by an as yet incomplete delineated patho-physiology. The therapeutic landscape for treatment of Multiple Sclerosis has rapidly changed over the last decade offering an increasing array of efficacious treatments for RRMS. Despite these advancements we continue to treat people with MS every day transitioning to secondary progressive MS, a disease state which represents a significant physical, cognitive, emotional, socio-economic burden on those with MS, their carers and upon healthcare systems which they become increasingly reliant upon. Therapies that alter the natural history of SPMS represent a highly significant unmet need. Aspirational treatment aims would include; 1. Prevention in the development of secondary progressive MS for patients with RRMS 2. In patients with SPMS would be to at least stop further progression but ideally reverse disability that had accrued.

	Regrettably, we are quite some time away from achieving this aspiration and I would argue that treatment enabling a significant reduction in disability progression represents a highly significant step change in current the management of secondary progressive MS.
8. 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.)	Clinical outcomes measures in progressive MS that are easily reproduceable, sensitive to change within the time period of current clinical trial as well as remaining impactful and meaningful to patients that correlate to long-term outcomes remain challenging. A variety of clinical outcome measures based on the expanded disability status scale (EDSS), Multiple Sclerosis Functional Composite (MSFC) score which is a multi-dimensional composite tool, as well as individual measures of cognition, Patient-reported outcome measures (PROMS) have all been utilised within clinical trials. It would be outside of the scope of this report to detail a comprehensive review of clinically significant measures, but I would consider a 20% Improvement in the disability progression as a clinically significant treatment response
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	I have no hesitation in stating that there is a clear and pressing unmet need for effective disease modifying therapies in patients with SPMS.
What is the expected place of the technology in current practice?	

10. How is the condition currently treated in the NHS?	As per MS Trust submission
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	The National Institute for Health and Care Excellence (NICE) has issued a clinical guidelines (CG186) in regard to the management of Multiple Sclerosis in adults (updated November 2019). This broadly covers the diagnosis, coordination of care, requirement for a comprehensive review as well as symptom management and rehabilitation. Additional guidelines have been issued by various international organisations which include European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) and European Academy of Neurology (EAN), and the American Academy of Neurology (AAN). The guidance regarding disease modifying therapies for the treatment of secondary progressive MS within all of these guidelines is understandably limited at best.
• 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 NICE guidelines for the management of adults with MS forms the benchmark for delivery of care, regional and local care pathway are highly variable throughout the UK. Financial, manpower and infrastructural constraints have not necessarily kept pace with the increasing complexity and delivery of current MS treatments. This has placed many clinical services in situations

	where they have had to prioritise their resources with a negative impact on patients with progressive MS with reduced direct clinical contact with healthcare professionals with a specialist interest in a MS. Considering the clinical and social needs associated with progressive disability patients with secondary progressive MS sit between both primary and secondary care agencies to a variable extent, often with lack of co-ordination in their care. Recent developments through sustainability transformational programs and the development of integrated care systems look to redress some of these imbalances but still require significant investment and cultural change of working practices. Therefore, I would argue that the pathway of care for patients with secondary progressive MS is not well defined and understandably there is quite a lot of variance in opinion between professionals as to how this could be best delivered utilising constrained resources.
• What impact would the technology have on the current pathway of care?	I believe it will represent a strong argument to stimulate further improvements in current care pathways
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	This is a novel innovation with regard to an effective treatment in slowing disease progression in SPMS and with appropriate service delivery planning could be introduced within current care pathways. However, some services may need support and/or uplift of existing infrastructure/manpower resources.

• How does healthcare resource use differ between the technology and current care?	This would represent step change in care as we have no current effective treatments in secondary progressive MS.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary care clinical setting / neurologist with a specialist interest in MS, supported with an integrated care system with primary care.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	To enable a smooth and clinically safe introduction and continued utilisation of Siponimod for treatment of secondary progressive MS will require several levels of engagement and investment. Firstly, education of patients and healthcare professionals in MS will be important to manage expectations. Secondly, MS clinical services are already quite significantly stretched regarding delivery of disease modifying therapies not only to RRMS but also more recently following the introduction of Ocrevus in primary progressive MS. The additional demand on clinical resources to review potentially eligible and treat patients with secondary progressive MS is not to be underestimated. Existing links with cardiology and ophthalmologic services are already in place with regard to fingolimod that is currently licensed for use for RRMS however, the increased clinical capacity requirement for similar

	support in the cohort of patients with secondary progressive MS will have additional impact on these clinical services.
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	See below
• Do you expect the technology to increase length of life more than current care?	Multiple Sclerosis is associated with a reduced life expectancy. Most of the mortality associated with MS is secondary to complications associated with disability and reduced mobility. It is therefore logical to assume that a treatment that reduces the rate of disability progression may well have a positive impact length of life although as yet we do not have any specific robust evidence in this regard to Siponimod or other treatments used in progressive MS.
• Do you expect the technology to increase health-related quality of life more than current care?	In addition to above it has been clearly demonstrated that quality-of-life deteriorates with increasing disability progression in Multiple Sclerosis and as such treatments that have an impact on reducing disability progression would increase the health-related quality of life more than the current levels of care. Moreover, the impact of MS on cognition is a significant driver towards loss of employment and subsequent impact on loss of independence and quality of life.

13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Not applicable
The use of the technology	
14. 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.)	Siponimod represents a novel treatment approach in the care of patients with secondary progressive MS that would be additional to current levels of care. Some of the practical implications have been covered in part already in my response to investment requirements needed to facilitate introduction and use of this treatment (see section 11). It is not in envisaged that there will be any requirements for other concomitant treatments to support treatment with Siponimod. Conversely, it could be argued that with effective treatment that slows the progression of MS that there may be a reduction or delayed use of the various symptomatic therapies targeting disease components such as spasticity or requirements for complex physiotherapy and rehabilitation. Pharmaco-vigilance and monitoring requirements will be set out in the European SMPC and will dictate additional clinical resources

15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Siponimod is indicated in the treatment of adult patients with SPMS with active disease which is delineated by presence of relapses or imaging features of inflammatory activity. Due to the prior lack of effective treatments for active SPMS, the use of MRI in patients to identify disease activity is uncommon in many UK centres. In consideration of the proposed indication along with increased frequency of clinical assessment of patients with secondary progressive MS it is likely to expect an increased utilisation of MRI imaging to capture evidence subclinical disease activity. The inclusion criteria for the clinical trial encompass patients up to and including an EDSS score of 6.5. I would not recommend any discrete EDSS level for treatment cessation. The rationale for such approach is based on such factors such as upper limb function and cognition which remain critical components of patients with secondary progressive MS and their quality of life even in the context of significantly reduced mobility. The EDSS score does not adequately capture changes in cognition or upper limb function at its upper range of scores. I would recommend that any rules informal or formal to delineate stopping treatment should be based in a shared decision-making approach with the patient and clinician experiencing the treatment of Multiple Sclerosis based on the appropriate risk benefit profile.
16. 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?	
17. 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?	I would consider Siponimod with its application of use in patients with secondary progressive MS to be innovative and addresses a significant clinical unmet need. Siponimod treatment in SPMS has demonstrated a reduced risk of confirmed increase in disability and improved cognition outcome measures. Moreover, this is paralleled with improvements in surrogate outcome measures which include reduced brain atrophy and lesion volume on MRI. This treatment therefore has the potential to make both direct and indirect positive benefits on health-related outcomes. The direct benefits include the reduction of disability and the associated socio-economic impact and resource utilisation of a less disabled cohort of MS patients. The indirect benefits are such that the increased clinical vigilance of patients with secondary progressive MS even if not eligible will enable greater symptomatic and supported care for the condition.
• Is the technology a 'step-change' in the management of the condition?	Yes, as described previously above

• Does the use of the technology address any particular unmet need of the patient population?	Yes, as described previously above
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Siponimod has a similar side effect and adverse event profile to fingolimod which is generally very well tolerated and as such with appropriately selected individuals would not expect Siponimod to represent a significant additional burden. The only caveat here is that the spectrum of patients treated for SPMS are likely to be an older age cohort where additional co-morbidities related to cardiovascular disease for example may be a consideration.
Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	Overall the clinical trial recruited patients that would be applicable to the UK population. The delivery of the trial from a safety perspective was commensurate with a phase III trial but it is expected that the SMPC will at a minimum reflect current UK practice that is currently being delivered with Fingolimod within RRMS
• If not, how could the results be extrapolated to the UK setting?	As per above
• What, in your view, are the most important outcomes, and were they measured in the trials?	Reduced confirmed disability progression and improved cognition outcome measures with synergistic MRI findings to support the clinical measures.

• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	As per above in regard to MRI features
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Not to my current knowledge but continued pharmaco-vigilance within a national framework remains important considering the potential use of Siponimod within a broader clinical cohort than delineated within the clinical trial paradigm.
20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
21. Are you aware of any new evidence for the comparator treatment(s) ?	No
22. How do data on real-world experience compare with the trial data?	Not applicable

Equality	
23a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
23b. Consider whether these issues are different from issues with current care and why.	Not applicable
Key messages	

25. In up to 5 bullet points, please summarise the key messages of your statement.

- Siponimod represents an innovative treatment for use in patients with active secondary progressive MS and addresses a major unmet need.
- The trial results demonstrate a reduction in confirmed disability progression and improved cognition outcome measures supported with synergistic para-clinical (MRI) outcome measures. These are important measures that are clinically significant to patients and their carers.
- I am enthusiastic that this drug has been licensed for its use in SPMS but education of patients and clinicians regarding what defines active secondary progressive MS will be important to manage expectations.
- If given a positive appraisal (re-) prioritisation and/or additional investment into MS clinical services will be required in some, if not most regions to ensure an clinically robust and safe implementation and delivery of Siponimod.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

.....

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

.....

NICE National Institute for Health and Care Excellence

NHS commissioning expert statement

Siponimod for treating secondary progressive multiple sclerosis [ID1304]

Thank you for agreeing to give us your views on this technology 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. Your response should not be longer than 10 pages.

Information on completing this expert statement

- 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	**Malcolm Qualie**
2. Name of organisation	**NHS England/NHS Improvement**

3. Job title or position	**Pharmacy Lead, Specialised Commissioning**
4. Are you (please tick all that apply):	☒ commissioning services for a CCG or NHS England in general? ☐ commissioning services for a CCG or NHS England for the condition for which NICE is considering this technology? ☐ responsible for quality of service delivery in a CCG (for example, medical director, public health director, director of nursing)? ☐ an expert in treating the condition for which NICE is considering this technology? ☐ an expert in the clinical evidence base supporting the technology (for example, an investigator in clinical trials for the technology)? ☐ other (please specify):
Current treatment of the condition in the NHS	
5. Are any clinical guidelines used in the treatment of the condition, and if so, which?	Yes, NICE have published NICE Guidelines - Multiple sclerosis in adults: management (CG186) although at the time of publication there was no pharmacological treatment for SPMS. NICE have also published several TA's relating to treatments for relapsing remitting MS (RRMS) and one for a treatment for primary progressive MS (PPMS). NHS England has issued an algorithm relating to the treatment of RRMS which can be found here https://www.england.nhs.uk/commissioning/spec-services/npc-crg/group-d/d04/
6. 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	NHS England has published a service specification for neuroscience centres (which in part includes MS services) which can be found here https://www.england.nhs.uk/commissioning/spec-services/npc-crg/group-d/d04/ As this specific form of MS has no directly acting treatment this would be considered a new service to the NHS. Therefore, current treatment of people diagnosed with SPMS focuses on management of symptoms

experience is from outside England.)	such as incontinence, fatigue, pain and depression. In addition, patients with SPMS with relapses may be treated with high-dose steroids.
7. What impact would the technology have on the current pathway of care?	Siponimod would represent a new treatment for people with SPMS, where historically there has been limited active therapy. It is estimated that there may be 30-40k patients with SPMS. As the evidence[1] suggests that siponimod slows the rate of deterioration in people with SPMS, demand for the treatment is expected to be high. Clinical feedback has included the importance of defining the patient population most likely to benefit from the treatment and some of the existing patients may be beyond the point where treatment will be deemed effective. Therefore, this is likely to have a significant impact on MS services in the NHS. It is thought that a proportion of patients who may be eligible for siponimod are likely to still be receiving treatment with a disease modifying treatment (DMT); this is because distinguishing between relapsing-remitting and progressive phenotypes of MS can be challenging, which, coupled with the lack of active treatments for SPMS, may result in patients remaining on DMTs as their disability progresses (transitioning from RRMS to SPMS).
The use of the technology	
8. To what extent and in which population(s) is the technology being used in your local health economy?	It is currently not being used outside any Pharma sponsored clinical trials.
9. Will the technology be used (or is it already used) in the	As there are limited treatment options for people with SPMS, they may not be routinely managed by neurologists; their symptomatic management is generally provided within the community, supported by MS nurses. If an intervention such as siponimod were available to a defined cohort of people with SPMS, it is likely that there will be significant demand for such treatment, putting pressure on nurses and MS clinics.

same way as current care in NHS clinical practice?	
• How does healthcare resource use differ between the technology and current care?	As stated above this is likely to have a significant impact on both activity and direct cost of medicine as it will not be replacing any current therapy. Currently used DMTs are commissioned by NHS England from acute provider trusts. More complex therapies, such as alemtuzumab and ocrelizumab, are provided by specialist neuroscience centres, or as part of an agreed provider network. Whilst MDT involvement is required for more complex treatments, based on existing experience with fingolimod used in the treatment of RRMS, it is not expected that routine MDT involvement in initiation of siponimod would be required.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	It should only be prescribed in secondary care Trusts where there is an appropriately constructed MS service as described in the NHS England algorithm.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Siponimod is expected to require a similar level of infrastructure to be in place as fingolimod, due to the similar pharmacology of these two agents. Dependent on the market authorisation granted, a patient may require a day-case appointment for cardiac monitoring when treatment is initiated. Regular blood tests, although may be less than those required for fingolimod, and a review by a clinical ophthalmologist will be required (hospital service) at approximately 3 months after the start of treatment due to the risk of macular oedema. As people with SPMS may not currently be managed within secondary care services, such monitoring would be an additional burden on existing services. On-going management of people with SPMS on siponimod, including supply and monitoring of treatment, may also be additional workload for existing services.
• If there are any rules (informal or formal) for	Not known

starting and stopping treatment with the technology, does this include any additional testing?	
10. What is the outcome of any evaluations or audits of the use of the technology?	There have been no audits on the use of this technology
Equality	
11a. Are there any potential equality issues that should be taken into account when considering this treatment?	Not aware of any
11b. Consider whether these issues are different from issues with current care and why.	n/a
Topic-specific questions	
12. [To be added by technical team if required, after receiving	

the company submission. For example, if the company has deviated from the scope (particularly with respect to comparators) – check whether this is appropriate. Ask specific, targeted questions such as “Is comparator X [excluded from company submission] considered to be established clinical practice in the NHS for treating [condition Y]?”] **if not delete highlighted rows**	

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

……

NICE National Institute for Health and Care Excellence

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

……

References

1. Siponimod versus placebo in secondary progressive multiple sclerosis (EXPAND): a double-blind, randomised, phase 3 study. Kappos, L. et al. The Lancet, volume 391, issue 10127, p 1263 – 1273. March 2018. Available at: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(18)30475-6/fulltext

Title: *Multiple sclerosis (secondary progressive) - Siponimod [ID1304]*

Produced by	Warwick Evidence
Authors	Peter Auguste, Research Fellow, Warwick Evidence
	Alexander Tsertsvadze, Senior Researcher, Warwick Evidence
	Mubarak Patel, Research Assistant, Warwick Evidence
	Chris Stinton, Senior Research Fellow, Warwick Evidence
	Felix Achana, Senior Research Fellow, Warwick Evidence
	Jacoby Patterson, Senior Researcher, Warwick Evidence
	Rachel Court, Information Specialist, Warwick Evidence
	Anna Brown, Information Specialist, Warwick Evidence
	Olga Ciccarelli, Professor of Neurology, University College of London
	Carl Counsell, Clinical reader, University of Aberdeen
	Xavier Armoiry, Honorary Clinical Research Fellow, Warwick Evidence
	Aileen Clarke, Professor of Public Health, Warwick Evidence
	Amy Grove, Assistant Professor, Warwick Evidence
Correspondence to	Dr Amy Grove
	A.L.Grove@warwick.ac.uk
Date completed	14/11/2019

Source of funding: This report was commissioned by the NIHR Systematic Reviews Programme as project number 12/97/79.

Declared competing interests of the authors

Prof. Carl Counsell received funding through Biogen-Idec, who provided some funding for a departmental MS nurse.

Prof. Olga Ciccarelli received consultancy fees from Novartis, Biogen-Idec and General-Electric, Genzyme, All payments were made to her employer, UCL Institute of Neurology. She also received reimbursement for attending a symposium from Novartis and ECTRIMS, and funds for research from the UK MS Society, EPSRC, UCLH and BRC.

Rider on responsibility for report

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

This report should be referenced as follows:

Auguste P, Tsertsvadze A, Patel M, Stinton C, Achana F, Patterson J, Court R, Brown A, Ciccarelli O, Counsell C, Armoiry X, Clarke A, Grove A. *Multiple sclerosis (secondary progressive) - Siponimod [ID1304]* Warwick Evidence, 2019: A Single Technology Appraisal.

Contributions of authors

Peter Auguste (Research Fellow) reviewed and critiqued the cost-effectiveness evidence and undertook additional analyses; Alexander Tsertsvadze (Senior Researcher) critiqued the indirect treatment comparisons and critiqued the clinical effectiveness evidenced; Chris Stinton (Senior Research Fellow) critiqued the decision problem; Amy Grove (Assistant Professor) provided the clinical summary, co-ordinated and conducted the critique of the clinical effectiveness evidence and co-ordinated the project and the report; Mubarak Patel (Research Assistant) Felix Achana (Senior Research Fellow) reviewed and critiqued the statistics and undertook any additional analyses; Jacoby Patterson (Senior Researcher) conducted the critique of clinical effectiveness evidence; Anna Brown (Information Specialist) and Rachel Court (Information Specialist) critiqued the company searches and undertook additional searches; Olga Ciccarelli (Clinical Professor), Carl Counsell (Reader) and Xavier Armoiry (Honorary Clinical Research Fellow) provided expert clinical advice; Aileen Clarke (Professor) reviewed and critiqued the company submission, clinical and cost-effectiveness evidence and report.

Table of Contents

LIST OF FIGURES

LIST OF TABLES

DEFINITION OF TERMS AND LIST OF ABBREVIATIONS

AE	Adverse events
ABN	Association of British Neurologists
AIC	Akaike information criterion
ARR	Annualised relapse rate
DMT	Disease modifying therapy
CDP	Confirmed disability progression
CEAC	Cost-effectiveness acceptability curve
CI	Confidence intervals
CrI	Credible intervals
CRD	Centre for Research and Dissemination
CS	Company submission
DMT	Disease-modifying therapies
EDSS	Expanded disability status scale
EM	Effect modifiers
ERG	Evidence review group
ESS	Effective sample size
EU	European
FAS	Full analysis set
FDA	Food and drug administration
GA	Glatiramer acetate
HCHS	Hospital and Community Health Service
NHS	National Health Service
HR	Hazard ratio
HRQoL	Health related quality of life
HSUV	Health state utility values
ICER	Incremental cost-effectiveness ratio
ICER 2019	Institute for clinical and economic review, 2019
IPD	Individual patients data
IM	Intramuscular
ITC	Indirect treatment comparison
ITT	Intention to treat
IV	Intravenous
LY	Life-years
LYG	Life-years gained
MA	Marketing authorisation
MAIC	Matching-adjusted indirect comparison
MS	Multiple sclerosis
MSWS-12	Multiple Sclerosis Walking Test-12
MSWS-24	Multiple Sclerosis Walking Test-24
MTC	Mixed treatment comparison
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
ONS	UK Office for National Statistics
PAS	Patient Access Scheme
PICOS	Patient, intervention, comparators, outcomes, and study design framework
PH	Proportional hazards
PML	Progressive multifocal leukoencephalopathy
PPMS	Primary progressive multiple sclerosis
PSA	Probabilistic sensitivity analysis
PSS	Personal social service
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life years
RCT	Randomised controlled trials
RMS	Relapsing forms of multiple sclerosis
RRMS	Relapsing-remitting multiple sclerosis
RoB	Risk of bias

SAE	Severe adverse events
SC	Subcutaneous
SMD	Standardised mean difference
SLR	Systematic literature review
SPMS	Secondary progressive multiple sclerosis
S1P	Sphingosine-1 phosphate
T25FW	Timed 25-foot walk
VAS	Visual analogue scale
WTP	Willingness-to-pay

1 SUMMARY

The objective of this report was to appraise the clinical and cost effectiveness of siponimod within its marketing authorisation (MA) for treating secondary progressive multiple sclerosis (SPMS) in adults. Currently, siponimod is not authorised for treating multiple sclerosis in the UK. It has been studied in clinical trials compared with placebo in people with SPMS. In 2019, the US Food and Drug Administration (FDA) approved siponimod for the treatment of relapsing forms of multiple sclerosis (MS), including clinically isolated syndrome, relapsing-remitting disease, and active SPMS, in adults.[1]

Siponimod is a selective agonist of the sphingosine-1 phosphate (S1P) receptors 1 and 5. The drug selectively binds to circulating lymphocytes which reversibly inhibits egress of lymphocytes from the lymph nodes, leading to a reduction in disease activity. It is administered orally. The CS Document B (page 14) states that siponimod is contraindicated for "*patients homozygous for CYP2C9*3 (CYP2C9*3*3) genotype (poor metaboliser)*". Therefore, before initiation of siponimod, patients must be genotyped for CYP2C9 to determine their CYP2C9 metaboliser status. The ERG note that this genotype testing has cost implications, as described in Section 5.4.1.

The company submission (CS) consisted of a systematic literature review (SLR), clinical efficacy and safety report of the pivotal trial evidence (EXPAND),[2] a Matching-Adjusted Indirect Comparison (MAIC) comparative clinical efficacy analysis of individual patients data (IPD) from the EXPAND study and aggregate published data from comparator treatment trials and a cost-effectiveness assessment.

1.1 Critique of the decision problem in the company's submission

In general, the CS decision problem matched the decision problem as specified by NICE in the final scope, although with some exceptions (See Table 1 and Section 3). Of note, the EXPAND[2] trial compared siponimod to placebo, not to one of the relevant comparators listed in the NICE final scope (e.g., interferon β-1b, disease-modifying therapies (DMT) used in UK clinical practice). However, the EXPAND trial remains relevant when considered in conjunction with other comparator treatment trials through the MAIC analysis presented in the CS (see Section 4.3 for ERG critique). The CS limited the decision problem to DMTs within their MA for relapsing-remitting multiple sclerosis (RRMS).

Table 1. ERG comparison of the NICE final scope and CS decision problem

	NICE	*CS*	ERG comment
Population	People with SPMS	*Adults with SPMS*	The population in the CS decision problem is restricted to adults. The exclusion of children is consistent with the MA; therefore, the ERG considers limiting to adults appropriate.
Intervention	Siponimod	*Siponimod*	-
Comparator	- Established clinical management, including DMTs used outside their MA - Interferon β-1b for patients with active disease, evidenced by relapses	*- Established clinical management, comprising ongoing RRMS DMTs* *- Interferon β-1b for patients with active disease, evidenced by relapses and/or MRI activity*	The CS limited DMTs within their MA for RRMS by excluding the treatments used outside their MA. The ERG note that DMTs are used outside their MA (as per NICE final scope) in clinical practice, therefore do not consider this limitation appropriate in the context of this appraisal. The ERG considers the addition of "*MRI activity*" to the definition of active disease (as a reflection of current clinical practice) to be appropriate, as outlined in clarification response A2b[3]
Outcomes	- Disability (e.g., EDSS) - Disease progression - Relapse rate and severity - Symptoms of MS - Freedom from disease activity - Mortality - Adverse effects of treatment - Health-related quality of life	*<u>Disability</u>* *- EDSS score* *<u>Disease progression</u>* *- Time to 3-month CDP* *- Time to 6-month CDP* *- Change from baseline in T2 lesion volume* *<u>Relapse rate and severity</u>* *- ARR* *- Time to first relapse* *- Proportion of relapse-free patients* *<u>Symptoms of MS</u>* *- Time to 3-month confirmed worsening of at =>20% from baseline in the T25FW* *- Change in score on the MSWS-12* *- Cognitive measures: PASAT; SDMT; BVMT-R*	The CS outcomes match those listed in the NICE final scope.

		<u>Freedom from disease activity</u> *- Number of T1 gadolinium-enhancing lesions* *- Number of new or enlarging T2 lesions* *- Percentage change in brain volume from baseline* *<u>Mortality</u>* *<u>Safety and tolerability</u>* *<u>Health related quality of life</u>* *- EQ-5D* *- MSIS-29*	
Subgroup(s)	Active disease, evidenced by relapses	*Active SPMS, as evidenced by relapse and/or MRI activity*	The ERG considers "*active SPMS*" to be appropriate as SPMS is in line with the population definition. The addition of "*MRI activity"* as a reflection of current clinical practice is appropriate.
NICE=National Institute for Health and Care Excellence; CS=company submission; PASAT=paced auditory serial addition test; SDMT=symbol digit modalities test; BVMT-R=brief visuospatial memory test revised; EQ-5D=European quality of life five-dimensions scale; MSIS=multiple sclerosis impact scale; MSWS=multiple sclerosis walking scale; T25FW=timed 25-foot walk test; SPMS=secondary progressive multiple sclerosis; MS=multiple sclerosis; EDSS=Expanded Disability Status Scale; MAIC=Matching-Adjusted Indirect Comparison; ARR=annualised relapse rate; DMT=disease-modifying therapy; ERG=evidence review group; CDP=Continuing Disease Progression			

1.2 Summary of clinical effectiveness evidence submitted by the company

The clinical effectiveness section of the CS is based on a systematic literature review (SLR), which included six randomised controlled trials (RCT) conducted in patients with SPMS (EXPAND, ASCEND, SPECTRIMS, IMPACT, North American [NA], and European [EU] studies).[2, 4-10] The EXPAND trial is described below (Section 1.2.1), the remaining five studies were double-blind placebo-controlled randomised trials of natalizumab (ASCEND study),[4] interferon beta-1b (EU study, NA study),[7-9] and interferon beta-1a (SPECTRIMS study, IMPACT study).[5, 6, 10]

1.2.1 Pivotal trial: EXPAND

The EXPAND[2] study was a double-blind phase-III placebo-controlled randomised trial which assessed the effectiveness and safety of siponimod. This was the only study included in the CS that provided clinical effectiveness data for siponimod in patients with SPMS. The effectiveness in the EXPAND trial was assessed using the outcomes measuring disability progression, relapse rates, and disease activity (MRI-related outcomes).[2]

Disability progression was assessed using the EDSS. The primary endpoint of EXPAND was time to 3-month CDP. CDP was defined as a 1-point increase in EDSS if the baseline score was 3.0-5.0 or a 0.5 increase if the baseline score was 5.5-6.5 .[2] Additional secondary endpoints included: time to 6-month CDP as measured by the EDSS, reducing frequency of confirmed relapses (including ARR) and HRQoL. MS relapse was defined as appearance of a new neurological abnormality or worsening of previously stable or improving pre-existing neurological abnormality, separated by at least 30 days from onset of a preceding clinical demyelinating event. Additionally, the abnormality must have been present for at least 24 hours and occurred in the absence of fever (<37.5°C) or known infection.

In EXPAND,[2] siponimod displayed a significant improvement compared with placebo for the following outcomes:

- Time to 3-month Confirmed Disability Progression (CDP) (Hazard Ratio [HR])=0.79; 95% CI: 0.65, 0.95)
- Time to 6-month CDP (HR=0.74; 95% CI: 0.60, 0.92)
- Annualised relapse rate (ARR) (HR= 0.45; 95% CI: 0.34, 0.59)
- Time to confirmed first relapse (HR= 0.54; 95% CI: 0.41, 0.70)
- Various cognitive measures and MRI-related outcomes (T2 lesion volume, brain volume, presence of gadolinium-enhancing lesions, new or newly enlarging T2 lesions).
- Siponimod was not significantly different from placebo for the following outcomes:
- Time to 3-month ≥20% worsening in Timed 25-Foot Walk (T25FW) from baseline (HR= 0·94; 95% CI: 0.80, 1.10)
- Between-group difference in the mean Multiple Sclerosis Walking Test (MSWS-12) score change from baseline at 12 months (-1.83; 95% CI: -3.85, 0.19)
- Between-group difference in the mean Multiple Sclerosis Walking Test (MSWS-24) score change from baseline at 24 months of follow-up (-1.23; 95% CI: -3.89, 1.44).

The occurrence of at least one serious adverse event (AE) in the siponimod group was slightly higher than in the placebo group (18% vs. 15%). Adverse events in the siponimod group included elevated liver transaminase concentrations, bradycardia, macular oedema, hypertension, varicella zoster virus reactivation, and convulsions, all of which have been described previously in the context of S1P-receptor modulation in MS.[2]

1.2.2 Mixed Adjusted Indirect Comparison

The company matched IPD from the EXPAND[2] study to aggregate-level data provided in publications of the five trials (ASCEND, EU study, IMPACT, NA study and SPECTRIMS)[4-10] to indirectly compare the effectiveness of siponimod and other therapies licensed and/or used in the treatment of SPMS in clinical practice (see, Section 4.3) the MAIC analysis).

The MAIC entailed the comparison of aggregate data from these trials with IPD from EXPAND for three key outcomes: 3-month CDP, 6-month CDP and ARR. The comparator trials included in the MAIC analyses generally had similar inclusion/exclusion criteria. However, there were specific differences in the inclusion and exclusion of patients with SPMS in the EXPAND trial and the other five trials. We will discuss this issue in more detail later in the report.

The MAIC results for time to 3-month CDP were not consistent across the comparator treatments. Siponimod significantly [redacted] time to 3-month CDP compared to intramuscular (IM) interferon β-1a (60 µg; [redacted]), but not compared to subcutaneous (SC) interferon β-1a at 22µg ([redacted]), SC interferon β-1a at 44µg ([redacted]), or SC interferon β-1b (250 µg; [redacted]).
Siponimod significantly [redacted] time to 6-month CDP compared to SC interferon β-1b (250 µg; [redacted]).

The ARR was significantly [redacted] with siponimod compared to SC interferon β-1a (22µg/44µg) ([redacted]), but not compared to interferon β-1a IM 60µg ([redacted]), IFNβ-1b SC 250µg ([redacted]), or natalizumab intravenous (intravenous [IV]) 300mg ([redacted]).

The ERG note that the results of the CS MAIC should be interpreted with caution due to:

- cross-trial heterogeneity in populations characteristics, and limited relevance of the comparator treatment trials' populations
- small effective sample size (ESS) after matching (constituting [redacted] of patients in the included trials)
- limited applicability of results to the target populations of patients with active SPMS
- possible residual unobserved differences and potential sources of bias after matching which have not been accounted for

- lack of an independent ERG assessment of the IPD from the EXPAND
- limited evidence of true effect modification in the MAIC.

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

1.3.1.1 SLR conduct and methods

- The CS presents a SLR aiming to identify studies on siponimod and SPMS and to be part of an indirect comparison relevant to the CS decision problem and NICE final scope
- The SLR was well conducted. The study eligibility criteria were based on the PICOS framework and were defined more broadly than the NICE final scope. The ERG consider this minimized the chance of missing relevant publications
- The ERG considers inclusion/exclusion criteria to be appropriate, although the possibility of publication bias due to excluding studies in languages other than English cannot not be ruled out
- The electronic searches for the SLR were adequate and the SLR methods were deemed to be appropriate. There were no major inconsistencies in the data extraction and the Risk of Bias (RoB) assessment tool was appropriate.

1.3.1.2 Pivotal trial: EXPAND

- The EXPAND study provided the only source of evidence for siponimod.[2] The study did not have a relevant comparator according to the NICE final scope (i.e., active treatment for relapsing MS/SPMS established in clinical practice)
- The EXPAND study used a rigorous design/methodology to ensure most important sources of bias were controlled for (central computer randomisation, adequate treatment allocation concealment, double-blinding, appropriate statistical analysis, ITT analysis)[2]
- Type-I error due to multiple testing was adjusted using the O'Brien-Fleming alpha correction. However, the ERG noted that some efficacy analyses of secondary outcomes were not adjusted for multiple testing (e.g., time to 6-month CDP, the number of T1 Gd-enhancing lesions, time to first confirmed relapse, SDMT score)
- The EXPAND trial had a 90% power to detect a (somewhat large but) pre-defined 30% between-group difference in the primary outcome (time to 3-month CDP)

- The baseline characteristics of the participants randomised in the EXPAND study were comparable between the groups; there were no major systematic differences in study or drug discontinuations across the two groups
- The occurrence of at least one serious AE in the siponimod group was slightly higher than in the placebo group (18% vs. 15%). The median follow-up period of the EXPAND study was 21 months, therefore, it may be too short for a more complete assessment of the comparative efficacy-safety profile of siponimod
- Due to lack of evidence, the ERG cannot assess the generalisability of the results of the EXPAND study to the target population of patients with active forms of SPMS in the UK.

1.3.1.3 MAIC

- The ERG note that the IPD used for the MAIC was not included in the CS or provided when requested during the clarification stage. Without IPD from the comparator trials, the ERG is concerned that there may still be residual unobserved differences and potential sources of bias even after matching
- Matching the EXPAND IPD to each comparator trial reduced the ESS to [redacted]. However, the ERG consider the ESS included in the economic base-case to be between [redacted]. The ERG note that when the ESS is markedly reduced, estimates become unstable due to a potential lack of population overlap and inferences depend heavily on a small number of individuals, where the integrity of the original randomisation procedure may be lost and bias may therefore be introduced
- The ERG are concerned that the ESS represents a substantial drop from the randomised sample size of EXPAND[2] (1651), and the sample included in the statistical analysis (1,645). The ERG note that participants were excluded without explanation from the unmatched and unadjusted EXPAND population in the MAIC scenario tables:
    - SPECTRIMS 1638[5, 6]
    - EU study 1638[8, 9]
    - NA study 1638[7]
    - ASCEND 1584/1645 [4]
    - IMPACT 1590/1550[10]
    - NA/EU study for ARR 1645[7-9]

The interpretation of findings presented from MAIC analysis should therefore, be interpreted with caution, due to unaccounted for cross-trial heterogeneity in population characteristics, a small ESS,

limited relevance of the comparator treatment trial populations and limited applicability of results to the target populations of patients with active SPMS.

Due to the uncertainty described above, the ERG performed exploratory network meta-analysis (NMA) for 3-month CDP, 6-month CDP and ARR (Section 4.4.1.1). The ERG NMA comprises a simultaneous analysis of all potential treatment options and makes full use of the available evidence within a single analysis, as opposed to the CS MAIC which analysed each comparator trial separately and therefore, adds valuable information.

The ERG NMA estimates generally favour siponimod over the comparator treatments, however the results of the NMA are not statistically significant with the exception of siponimod versus SC interferon β-1a 44 µg for the 3-month CDP outcome (HR 0.79 95% CI 0.66, 0.95) and siponimod versus SC interferon β-1a 22 µg and 44 µg for the ARR outcome ([RR 0.65 95% CI 0.47, 0.91], [RR 0.65 95%CI 0.46, 0.92]). A comparison of the results of the CS MAIC and ERG NMA are provided in Section 4.5. The estimates generated from the ERG NMA for 6-month CDP and ARR are used in the ERG base-case in the economic appraisal.

1.4 Summary of cost-effectiveness submitted evidence by the company

The economics section of the CS included a SLR of the economic evidence and resource use and costs, a separate SLR to identify studies that measured health-related quality of life (HRQoL) in people with MS, and an electronic Markov model built in Microsoft Excel®.

The SLR did not identify any cost-effectiveness analyses that included siponimod versus any DMTs for treating people with SPMS. The majority of studies included interferon β-1b in the economic analysis.

The company constructed a Markov model to estimate the cost-effectiveness of siponimod compared to interferon β-1b (Extavia®) for treating people with SPMS. Information required on the natural history was based on data from the EXPAND trial[2]and the London Ontario database.[11] SPMS disease progression was depicted using the 10 EDSS levels ranging from EDSS 0 to 9 (as described in Section 4.2.1.5). The hypothetical population entering the model was distributed across EDSS levels 2 to 7, reflecting the EDSS distribution of participants in the EXPAND trial.[2]

During each annual cycle, people either remained in the same SPMS EDSS health state, progressed to a more severe EDSS state, regressed to a less severe state, or died. Additionally in each cycle, people experienced relapses, treatment-related AE or discontinued treatment, all of which were captured in separate EDSS health states. People discontinued DMTs when they progressed to EDSS ≥7, then followed a natural history progression.

DMTs delayed the progression of SPMS and reduced the frequency of relapses. Treatment efficacy for siponimod compared to interferon β-1b was based on the MAIC conducted by the company (see Section 4.4 for ERG critique). Information about health state utility values for SPMS by EDSS level, were based on information from the EXPAND trial,[2] supplemented with health state utility values from Orme et al., (2007)[12] which were derived from utility values from the UK MS survey.[12] Decrements for people who experienced AE were obtained from previous MS technology appraisals. Age- and gender-specific all-cause mortality rates for a UK general population were derived from the UK Office for National Statistics (ONS) data,[13] and adjusted using the mortality rates obtained from Pokorski et al., (1997).[14] It was assumed that increase in mortality found for people with RRMS can be applied to people with SPMS.

Information about resource use and their unit costs were obtained from published literature, (British National Formulary,[15] PSSRU,[16] National Health Service [NHS] reference costs).[17] Costs related to genotype testing, drug acquisition, administration and monitoring, disease management, treating relapses, and treating AE were included in the economic analysis.

The analysis was undertaken from the NHS and Personal Social Service (PSS) perspective. Health outcomes included time in each EDSS state, number of relapses, life-years (LY) and quality-adjusted life-years (QALYs) gained over a 50-year time horizon. Cost outcomes included disease management costs, drug acquisition, administration and monitoring, costs for treating relapses and costs associated with treating adverse events. The results were presented as an incremental cost-effectiveness ratio (ICER) expressed as cost per QALYs gained. Both costs and effects were discounted at 3.5% per annum. The company undertook a number of sensitivity analyses including probabilistic sensitivity analysis (PSA), and scenario analysis to determine the robustness of the base-case results by making changes to model inputs and assumptions. Additionally, the company undertook subgroup analysis of people with active SPMS (see Section 4.2.6 for subgroup definition). Conservative estimates were used in the absence of information for this subgroup.

Base-case deterministic results demonstrated that treatment siponimod was more costly and expected to yield more QALYs than treatment with interferon β-1b, which resulted in an ICER of approximately [redacted] per QALY. Sensitivity analysis results showed that the HR for 6-month CDP was the most influential model input with the greatest impact on the ICER. The PSA indicated that at a £30,000 willingness-to-pay (WTP) threshold for a QALY, siponimod had a [redacted] probability (according to the economic model) of being cost-effective when compared to interferon β-1b. Results for the active SPMS subgroup analysis showed that siponimod is approximately [redacted] more expensive than interferon β-1b and expected to yield 0.29 and 1.35 more LYs and QALYs, respectively, which equated to approximately [redacted] per QALY.

1.5 Summary of the ERG's critique of cost-effectiveness evidence submitted

The ERG did not identify any major errors in the company's model. There were some discrepancies between the company's model and CS document B with regards to the information contained in their base-case, but largely the results reported in the document reflected those in the model. However, the ERG raise the following concerns and uncertainties:

- The company's MAIC results for CDP and ARR appeared to be optimistic, potentially overestimating the benefit of siponimod compared to interferon β-1b
- Transition probabilities based on a natural history cohort were derived from the EXPAND trial[2] and supplemented with information from the London Ontario database,[11] which showed that people may regress or have improvement in their disability. Though the treatment effect is not applied to backward transition probabilities, there is still some indirect benefit derived
- A Weibull parametric curve was fitted to the discontinuation data. Based on Akaike information criterion (AIC), visual inspection and clinical plausibility, the exponential distribution also provides plausible estimates
- The treatment effect for siponimod compared to interferon β-1b was applied as a probability as opposed to a rate
- Health state utility values in the base-case were derived from HRQoL information collected in the EXPAND trial[2] and supplemented with utility values obtained from Orme et al., 2007.[12] The ERG consider that due to the sample size of people providing data for each EDSS state, the results from the EXPAND trial[2] may not be representative/generalisable to an SPMS population

- At clarification stage, the company stated that the cost for genotyping will be borne by the company, however in the model a conservative assumption is made that the costs will be borne by the NHS
- The base-case assumed that health state management costs are similar for people with RRMS and SPMS, thus the company used health state costs for people receiving treatment for RRMS. The ERG are aware that specific SPMS health state costs are available.

1.6 ERG commentary on the robustness of evidence submitted by the company

1.6.1 Strengths

The company's SLR of the cost-effectiveness literature was methodologically sound, and was likely to identify the evidence available. The company's economic model was logical and reflected a similar approach as seen in other MS appraisals. The process of identifying model input parameters, as well as the selection of inputs for the model was transparent, justified and similar to other previous technology appraisals. The economic analysis conformed to the NICE reference case. To have a workable model the assumptions made by the company appeared to be plausible.

1.6.2 Weaknesses and uncertainty

We identified several weaknesses and uncertainties in the CS Document B and economic model:

- In general, the results in the CS Document B were in good agreement with those reported in the company's economic model. However, there were instances in the base-case where the model inputs were not consistent to those in the economic model.
- Each cycle of the model requires information about the patient disposition to calculate costs and utilities across each EDSS state for the model time horizon, and the company submission left us unclear on the logical steps required to understand the mechanics of the model.
- There was little flexibility in the economic model (e.g., 'user inputs') for the ERG to make changes to the inputs

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

1.7.1 Exploratory analyses related to cost-effectiveness

The ERG undertook exploratory analyses that compared siponimod versus interferon β-1b by making changes to the company's model inputs, all of which formed the ERG's preferred values and/or assumptions, made simultaneously:

- ERG's NMA results for 6-month CDP (HR=0.80, 95% CI: 0.57, 1.13) and ARR (HR=0.65, 95% CI: 0.46, 1.04)
- Natural history transition probabilities based on the London Ontario dataset derived by the company
- Exponential distribution fitted to discontinuation data
- Treatment effect for siponimod compared to interferon β-1b applied as a rate as opposed to a probability
- Health state utility values obtained from Orme et al., (2007)[12]
- Costs of £35 for genotyping borne by the company
- Health state management costs obtained from TA320.[18]

Based on the ERG's preferred inputs, the deterministic results show that siponimod compared to interferon β-1b was more expensive and yielded more QALYs, resulting in an ICER of approximately [redacted] per QALY. PSA results demonstrated that at a WTP threshold of £30,000 per QALY siponimod had a [redacted] probability of being cost-effective.

2 BACKGROUND

2.1 Critique of company's description of underlying health problem.

2.1.1 Disease overview

The CS provides an adequate disease overview and description of the pathogenesis of MS in Document B, Section B.1.3.1 (pages 15-17). It provides a description of the underlying health condition with emphasis on the disease course over time. The CS states that the overall pathophysiology of MS is complex and not completely understood. The CS does not provide any information regarding the environmental and genetic factors which have been associated with an increased risk of developing MS.[19]

2.1.1.1 Types of MS

The CS provides a detailed description of three broad forms of MS and states that MS is classified by the pattern and frequency of relapses and the rate of progression. The ERG notes that MS can develop and progress in three major forms: (1) relapsing–remitting MS (RRMS), (2) primary progressive MS (PPMS) and (3) secondary progressive MS (SPMS).[19] The CS provides a useful diagram (CS Document B, Figure 1) that details the types of MS and the "*transition zone*" between relapsing forms of MS (RMS) which overlap significantly with SPMS. The ERG have reproduced this diagram in Figure 1.

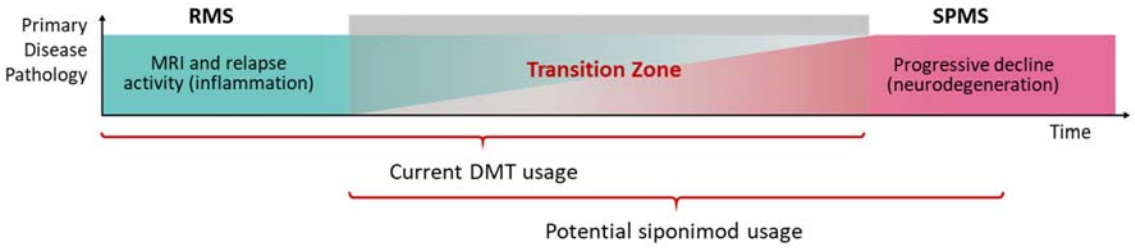


Figure 1. MS pattern over time, reproduced from CS Document B Figure 1

The CS describes the MS pattern over time as a "*continuum*" but notes that both inflammation and neurodegeneration are present in all forms of the disease (Document B, page 16). The CS continues that "*approximately two-thirds of patients initially diagnosed with RRMS will transition to SPMS within a period of 30 years*". The ERG verified the citations included by the company, and further note that transition from RRMS to SPMS occurs in 60-70% of patients.[20]

2.1.2 Epidemiology

MS is a lifelong condition which affects over 100,000 people in the UK.[21] The peak incidence of MS in the UK occurs between 40 and 50 years of age.[22] The CS (Document B page 16) states that RRMS affects 85% of newly diagnosed patients, the ERG note that the citations included make reference to the MS Trust website and a publication which reports data from a National Multiple Sclerosis Society survey conducted in the USA.[20] The ERG prefer to cite international data from the WHO Multiple Sclerosis Atlas (updated 2013), however, the given statistics are similar.[23]

The MS Trust, report that around 58% of people with RRMS will develop SPMS 15–20 years after diagnosis. The CS states that approximately 43,000 people in the UK have SPMS (CS Document B, page 16). The ERG verified that the citations for this figure refer to UK and Isle of Man studies.[12, 24] Of people with MS, 10-15% are diagnosed with PPMS, where symptoms get progressively worse over time, rather than appearing as relapses. The ERG identified a publication by Mackenzie and colleagues, which reported the incidence and prevalence of MS in the UK in 1990-2010. The publication estimated that 126,669 people in the UK were living with MS and there were 6,003 with newly diagnosed cases in a year.[25] This is currently the most comprehensive study regarding the prevalence and incidence of MS in the UK. The MS Society produced an estimate in 2018 using data from the Mackenzie publication[25] which suggested that there are over 110,830 people with MS in the UK, and approximately 5,190 people newly diagnosed.[26]

2.1.2.1 Presentation and diagnosis

In Document B (page 16), the CS states that the definition of SPMS varies as there is "*no clear clinical, imaging, immunologic, or pathologic criteria to determine a so-called "transition point" when RRMS converts to SPMS*". During clarification (A1), the ERG asked "*how SPMS was defined in the CS*". The company confirmed that the CS defined SPMS as per the definition provided in the pivotal trial EXPAND[2] (A1 response "*SPMS was defined by a progressive increase in disability (of at least 6 months duration) in the absence of relapse or independent of relapses*").

The ERG note the difficulties in detecting a transitional period from RRMS to SPMS due to overlapping types of RRMS to SPMS and uncertainties in the diagnosis of SPMS. Typically, SPMS follows RRMS but the disease course is progressive, with or without temporary relapses, remissions and plateaus in symptoms.[20] Therefore, the transition from RRMS to SPMS is gradual and SPMS is often diagnosed retrospectively.[20] The CS states that a mean of 2.9±0.8 years is a typical length of time for the uncertainty

of whether a patient has transitioned to SPMS (CS Document B, page 16). The ERG clinical advisor confirmed the gradual transition between the two types of MS.

2.1.2.2 Clinical symptoms

The CS adequately describes a range of symptoms experienced by patients with MS (CS Document B, page 17) including "*pain, muscle weakness or spasticity, chronic fatigue, unsteady gait, speech problems, incontinence, visual disturbance and cognitive impairment*" and "*decline in mobility*". However, the ERG note two additional clinical symptoms, [27 20 20 20] sensory and sexual disturbances.[23] The CS states that the following psychological symptoms: distress, quality of life, depression and anxiety, are worse in SPMS than both RRMS and PPMS (CS Document B, page 17).

2.1.2.3 Imaging features

The CS does not provide a description of the MRI sequences used for characterising MS severity and progression. Typically, the type of lesions found include: T2 lesions, T1 lesions and Gd+.[19] The ERG note that newer and more complex imaging sequences are available (i.e., phase sensitive inversion recovery), which enable improved understanding of pathophysiology and diagnosis specificity.[28]

2.1.2.4 Diagnostic criteria

The CS provides an overview of the variability of SPMS diagnosis. In addition, the ERG note that a diagnosis of MS is a clinical one, with supportive roles for neuroimaging and paraclinical findings.[19] There is a requirement for the diagnosis of MS to demonstrate central nervous system lesions disseminated in time and space. The McDonald criteria, revised in 2010, and updated in 2017, continue to form the standard diagnostic tool for investigating suspected MS in research settings and, to a more flexible degree, in clinical practice.[29] The ERG note that the McDonald criteria were the diagnostic criteria used in the pivotal trial (EXPAND) for siponimod.[2]

2.1.3 Measurement of disability

The CS Document B, Section B.1.3 does not describe how disability is measured in MS (e.g., EDSS, T25FW, 9-HPT, MSFC, PASAT or SDMT [Section 4.2.1.5]). Quantification of disability in MS has been used extensively to standardise characterisations of functional disease progression. The ERG note that

EDSS is typically used to measure disease progression in MS. It quantifies disability in eight functional systems: pyramidal, cerebellar, brain stem, sensory, bowel and bladder, visual and cerebral/mental function.[19] An EDSS score of 0.0 indicates normal neurology with no impairment in any system; an EDSS score of 4 suggests full ambulation without aid despite relatively severe disability; a score of 6 suggests needing unilateral support to walk 100 m; and a score of 7 suggests wheelchair confinement, with an inability to walk > 5 m with support.[19] The ERG highlight that EDSS is scored by a clinician and therefore, is at risk of subjective bias, it is also argued by some professionals that the scale is more of a categorical one representing a qualitative relationship to level of disability rather than a strictly numerical one with a linear relationship to actual disability.[30]

2.1.4 Burden of MS

The ERG consider that the CS description of the physical, psychological and economic impact of MS on the patient and careers is adequate (CS Document B, page 17). The ERG consider the assumptions around the societal and healthcare burden of MS are reasonable.

2.2 Critique of company's overview of current service provision

A critique of the company decision problem is provided in Section 3. The CS focuses on treatments for patients with SPMS. However, the CS states that there are a number of DMTs which have been recommended for use in MS, but that "*these almost exclusively apply to patients with RRMS*" (CS Document B, Section B.1.3.3 page 19). The CS argue that interferon β-1b is the "*only current option for patients with SPMS, as well as RRMS, but is only recommended in the case of patients experiencing continuing relapses*".[52] The ERG note that the CS citation for this statement refers to the NICE TA527 (Beta interferons and glatiramer acetate for treating multiple sclerosis Technology Appraisal guidance). The ERG question the company statement that interferon β-1b is the "*only current option for patients*", and suggest that a range of DMTs could potentially be used in the NHS for patients with SPMS (as reflected in the comparators listed in the NICE final scope). During clarification (response A2) the company later state that "*interferon β-1b is the only treatment specifically reimbursed for any patients with SPMS (TA527)"* which the ERG consider to be a more appropriate statement.

The company suggest that the clinical trial evidence demonstrates that interferon β-1b reduces relapse risk in patients with SPMS but has not been shown to be able to significantly slow disability progression versus placebo (CS Document B page 19).[7, 31] The ERG queried this statement during clarification

(Clarification Question A5) as we considered that "*the same statement could be made for interferon β-1a drugs as three RCTs (SPECTRIMS, Nordic SPMS, and IMPACT trials) showed [that] the drugs failed to slow disability progression (on EDSS) in SPMS."* In response to clarification question A5 "*Can the company state why interferon β-1a drugs were not included as a treatment option in the CS clinical effectiveness sections?"* the company stated that *"Avonex® and Rebif® [interferon β-1a] are still considered as treatment options for patients with RRMS in CS Document B Section B.1.3.3, as shown in the footnote of Figure 2 (Page 19)."*

The CS provides no further description of current service provision. However, all DMTs which are approved for use in the NHS are listed in CS Document B Figure 2, page 19. This figure references the NHS England treatment algorithm[32] which overlaps with interferon β-1b described by the company as the "*only*" treatment option. The ERG clinical expert states that the NHS England treatment algorithm included in the CS "*mostly*" provides an appropriate reflection of clinical practice. And noted that patients often switch "*agents in sequence"* according to patient preferences or intolerance/lack of efficacy of previous treatment. See Section 4.3 for ERG critique of comparators included in the MAIC.

The CS later describes three DMTs which are licensed for RMS (ocrelizumab, cladribine and interferon β-1a) and provides various descriptions as to why the company consider that they are not deemed to be a treatment option for patients with SPMS (CS Document B, page 19). The ERG disagrees with the CS on ocrelizumab, cladribine, and interferon β-1a as irrelevant treatment options. This discrepancy reflects the lack of clear criteria to determine the transition point for when RRMS patients converts to SPMS. Ocrelizumab, cladribine, and interferon β-1a are used along the continuum of RRMS-SPMS, especially when a differential diagnosis between the two is difficult (see Section 2.1.2.1).

2.2.1 Unmet treatment need

The CS Document B page 20, focuses on an unmet treatment need in SPMS and concludes that there are "*currently no licensed or proven treatments for patients with SPMS experiencing disability progression independent of relapses*" and note that drugs can be prescribed for symptom management, as outlined in CS Document B Figure 2.

The CS later states that siponimod would be the "*first treatment to be recommended by NICE that can slow disability progression for patients with SPMS and the first for use in all patients with SPMS*". The action of siponimod is described in the pivotal trial publication by Kappos et al, 2018.[2] According to

Kappos and colleagues, siponimod selectively modulates sphingosine-1-phosphate receptors S1P1 and S1P5 which reduces the egress of lymphocytes from lymphoid tissues and prevents recirculation of peripheral lymphocytes to the CNS.[2] The CS states that S1P1 and S1P5 receptors are involved in regulation of immunomodulatory/anti-inflammatory, pro-myelinating and neuroprotective effects.[33, 34] and that siponimod is a close structural analogue of S1P (CS Document B, page 18).

The CS Document B (page 14) states that siponimod is contraindicated for "*patients homozygous for CYP2C9*3 (CYP2C9*3*3) genotype (poor metaboliser)*". Therefore, before initiation of siponimod, patients must be genotyped for CYP2C9 to determine their CYP2C9 metaboliser status. The ERG note that this genotype testing has cost implications, as described in Section 5.4.1.

2.3 Marketing authorisation

The ERG note that the FDA approved siponimod for RMS, which includes clinically isolated syndrome, RRMS and active SPMS in March 2019.[1] An application for a licence to market siponimod as a treatment for SPMS was submitted to the European Medicines Agency (EMA) in September 2019, and a decision is expected December 2019.

2.4 Equality considerations

The CS state that "*the technology is unlikely to raise any equality concerns, considering that the technology will not exclude certain patient populations*" (Document B, B.1.4 page 20). The ERG consider this to be appropriate.

3 CRITIQUE OF COMPANY DEFINITION OF DECISION PROBLEM

The ERG provide a comparison of the NICE final scope and CS decision problem in

Table 2.

3.1 Population

The NICE final scope defined the population as "*people with secondary-progressive multiple sclerosis*", with the remit/appraisal objective as "*To appraise the clinical and cost effectiveness of siponimod within its marketing authorisation for treating secondary progressive multiple sclerosis in adults*." The population in the company decision problem (CS Document B, Table 1, page 12) is restricted to adults, with the CS stating that "*siponimod is anticipated to be licensed for adult patients with SPMS*". The exclusion of children is consistent with the MA; therefore, the ERG considers limiting to adults to be appropriate.

3.2 Intervention

The intervention listed in the company decision problem matches that in the NICE final scope: siponimod.

3.3 Comparators

The comparators listed in the decision problem differ from the NICE final scope. The final NICE scope defined the comparators as:

(1) "Established clinical management, including disease-modifying therapies used outside their marketing authorisations" and

(2) "Interferon β-1b for patients with active disease, evidenced by relapses".

The CS decision problem limits point 1 to "*established clinical management, comprising ongoing RRMS DMTs*". Therefore, excludes all other DMTs used outside of their MA. The ERG considers that the justification provided by the company for limiting the DMTs only to RRMS DMTs is not adequate. The company state that "*patients start DMTs in RRMS and continue to use them during the transition, while being suspected of SPMS*" which the ERG clinical advisor confirms is accurate, but this statement does not provide an explanation of their decision to limit the comparators. The company provide the following rationale for the difference in comparators "*Interferon β-1b is currently the only option specifically for treatment for patients with SPMS, and is therefore considered the most relevant comparator within established clinical management*". The ERG do not consider interferon β-1b to be the only/most relevant comparator, as other DMTs could potentially be used to treat patients in the NHS (as descried in the NICE final scope "disease-modifying therapies used outside their marketing authorisations") (see Section 2.2).

The CS decision problem extends point 2 to "*Interferon β-1b for patients with active disease, evidenced by relapses and/or MRI activity*". The company suggest that *" 'evidenced by relapses' reflects practice ~15–20 years ago.*" The ERG considers the addition of MRI activity to the definition of active disease (as a reflection of current clinical practice) to be appropriate.

3.4 Outcomes

The CS decision problem outcomes partially match those in the NICE final scope, with one exception. The NICE final scope specifies "*relapse rate and severity (for those with active disease)".* Whereas relapse rates and severity in the company decision problem are not limited to those with active disease. The rationale provided by the company highlights the use of data which is available in the pivotal trial EXPAND.[2] The CS states that "*measures of relapse rate and severity are assessed for all patients, regardless of disease activity at baseline".* The company continue… "[redacted] *of patients identified as non-Active at baseline in the placebo arm [of the EXPAND[2] trial] went on to exhibit relapses in the trial, highlighting the difficulties in accurately defining a patient as non-Active*" (CS Document B, Table 1, page 12). The ERG consider this rationale acceptable as it reflects the data collected in the key trial. However, the ERG note that a subgroup analysis of only those with active disease is subsequently presented in CS Document B Section B2.7 (page 56).

3.5 Subgroups to be considered

The subgroup defined in the NICE final scope is "active disease, evidenced by relapses", this differs from the company decision problem as the company limits subgroups to "*active SPMS, as evidenced by relapse and/or MRI activity".* The ERG consider the addition of "*evidenced by relapse and/or MRI activity"* to be an appropriate change as described in Section 3.3.

During clarification (A3), the ERG queried whether SPMS with non-active disease should be considered a subgroup, the company responded that they "*do not wish to consider 'SPMS with non-active disease' as a subgroup"* they further note that *"…determination of activity in clinical practice is difficult, especially when patients being considered for siponimod would be expected to be treated with a DMT for RRMS…a patient with non-active disease at baseline may develop activity during a clinical trial, meaning it is not possible to define a subgroup a priori with 100% certainty, resulting in inaccurate or uninterpretable efficacy result for a non-active SPMS subgroup population*". The company further note that "*a specific subgroup population of active SMPS was additionally presented, [in the CS] to align with the US FDA licence for siponimod in active SPMS patients*".

3.6 Other relevant factors

The company state that a "confidential simple discount Patient Access Scheme (PAS) provides siponimod at a fixed net price of £[redacted] per pack of 28 tablets. This represents a [redacted] discount from the list price. Annualised cost of siponimod at with-PAS price: £[redacted]"

Table 2. ERG comparison of the NICE final scope and the CS decision problem

	NICE	*CS*	ERG comment
Population	People with SPMS	*Adults with SPMS*	The ERG considers the exclusion of children and young people to be appropriate
Intervention	Siponimod (Mayzent®)	*As per scope*	-
Comparator	• Established clinical management, including disease-modifying therapies used outside their marketing authorisations • Interferon β-1b for patients with	• *Established clinical management, comprising ongoing RRMS DMTs* • *Interferon β-1b for patients with active disease, evidenced by relapses and/or MRI activity*	No clear rationale provided for decision to limit only to RRMS DMTs The ERG considers the addition of MRI activity to be appropriate

	active disease, evidenced by relapses		
Outcomes	•Disability (for example, EDSS) •Disease progression •Relapse rate and severity (for those with active disease) •Symptoms of MS such as fatigue, cognition and visual disturbance •Freedom from disease activity •Mortality •Adverse effects of treatment •Health-related quality of life	• *Disability* • *Disease progression:* • *Relapse rate and severity* • *Symptoms of MS* • *Freedom from disease activity* • *Mortality* • *Safety and tolerability (adverse effects of treatment)* • *HRQoL*	-
Subgroups to be considered	• Active disease, evidenced by relapses	• *Active SPMS, as evidenced by relapse and/or MRI activity*	The ERG considers the addition of MRI activity to be appropriate

NICE=National Institute for Health and Care Excellence; CS=company submission; PASAT=paced auditory serial addition test; SDMT=symbol digit modalities test; BVMT-R=brief visuospatial memory test revised; EQ-5D=European quality of life five-dimensions scale; MSIS=multiple sclerosis impact scale; MSWS=multiple sclerosis walking scale; T25FW=timed 25-foot walk test; SPMS=secondary progressive multiple sclerosis; MS=multiple sclerosis; EDSS=Expanded Disability Status Scale; MAIC=Matching-Adjusted Indirect Comparison; ARR=annualised relapse rate; DMT=disease-modifying therapy; ERG=evidence review group; CDP=Confirmed Disability Progression

4 CLINICAL EFFECTIVENESS

4.1 Critique of the methods of review(s)

The CS undertook a systematic review of evidence which is relevant to the company's decision problem; a SLR to identify relevant clinical evidence describing the effectiveness, safety and tolerability of pharmacological treatments for patients with SPMS, and an SLR of cost-effectiveness evidence (see Section 5). The processes (methods and number of reviewers) for study selection and data extraction were described in the CS Appendix D and appear to be appropriate.

Overall, the ERG consider the chance of systematic error in the clinical effectiveness SLR to be low.

4.1.1 Searches

Searches in an appropriate set of bibliographic databases were undertaken in October 2018 and updated in March 2019. Suitable terms, including those for siponimod, were included and combined appropriately. Searches also included terms for other SPMS interventions, resulting in a broad search suitable for retrieving non-siponimod studies in SPMS. In addition, a reasonable range of grey literature sources including three trials registers, several HTA websites and relevant conferences (limited to the past four years) were searched or browsed. These are reported with search terms used.

As new records are not being added to the HTA Database while it moves from the Centre for Research and Dissemination (CRD) to INAHTA, a targeted web search (using Google or an equivalent search engine) for Health Technology Assessments of siponimod would have been appropriate. The ERG note that the literature searches did not identify the recently published report by ICER,[35] but (as noted in the response to clarification question B1), this report was published after the company's update searches for both clinical and cost-effectiveness were undertaken.

The ERG undertook targeted searches of trial databases and checked the included studies of related systematic reviews, and did not identify other studies that met the eligibility criteria for the MAIC. The ERG requested four documents from the company which were not included in the CS reference pack. These were supplied during clarification (question 1).

4.1.2 Inclusion criteria

The eligibility criteria for study inclusion and exclusion were defined according to patient, intervention, comparators, outcomes, and study design (PICOS) framework (CS Appendix D, Table 11, page 35). Briefly, the inclusion criteria were comparative English-language publications (full text or abstract) of analytical studies (i.e., randomised/non-randomised trials, case-control, cohort, and cross-sectional studies) in adults (≥18 years) diagnosed with SPMS and treated with siponimod, interferon β-1b, interferon β-1a, other established active treatment (including RRMS DMTs), best supportive care, or placebo. Although other SLR/NMA were not eligible to be included in the CS SLR, their bibliographies were used and hand-searched for additional articles of relevance to the company SLR. An eligible study had to report at least one of the outcomes in the area of:

- disability
- disease progression
- symptoms of MS (e.g., fatigue, cognition, visual disturbance)
- relapse occurrence/severity
- disease activity (MRI parameters)
- mortality
- health-related quality of life
- and/or adverse events.

Full details of the study eligibility criteria are provided in CS Appendix D (Table 11, page 35). The ERG considers the inclusion criteria to be appropriate, although the possibility of publication bias due to excluding studies in languages other than English is noted.

The study selection process was performed at abstract and full-text levels. Initially, two independent reviewers screened all the studies identified in the searches of bibliographic records at abstract level. Full texts of all potentially eligible abstracts which passed to the second stage of screening were reviewed by two independent reviewers using the pre-specified eligibility criteria. Disagreements regarding inclusion/exclusion of any given abstract or a full-text record at both levels of screening were discussed and reconciled between the two reviewers or with a help of a third reviewer. The list of excluded studies (at full text review) with reasons for exclusions were provided for the original SLR (CS Appendix D, Table 13, page 44) and the update (CS Appendix D, Table 15, page 63). The company provided a graphical display of the study selection process using a PRISMA study flow diagram for the original SLR (CS Appendix D, page 37) and updated SLR (CS Appendix D, page 62).

The ERG considered the study selection methodology, process, and reporting quality to be acceptable.

4.1.3 Critique of data extraction

All full texts which were deemed eligible for inclusion in the SLR were extracted by one reviewer and checked by a second reviewer. Where multiple publications described a single trial, data were extracted into a single entry in a data extraction table to avoid double counting of patients. Each publication was referenced to indicate that more than one publication contributed to the study entry (CS Appendix D, page 35). The ERG consider this to be appropriate.

4.1.4 Quality assessment

The company used the NICE checklist (Appendix D, page 143) to assess RoB of the one included trial of siponimod identified in the SLR (see Section 4.2). The EXPAND^2 trial was assessed across the domains of randomisation, allocation concealment, blinding (participants, study personnel, and outcome assessors), similarity of groups at baseline, sample attrition/incomplete outcome data (Intention To Treat [ITT] analysis, sensitivity analysis), selective outcome reporting (CS Document B, page 38). The CS assessed all domains of the EXPAND trial to be at low RoB, although the company do not state if the RoB assessment was performed by two independent reviewers.

Two ERG reviewers independently assessed the RoB of the EXPAND^2 trial using the same tool as was used in the CS, since it covers the same domains used in the Cochrane RoB tool for RCTs.[36] Given our independent assessment (see Table 3), the ERG agree with the CS that the EXPAND^2 trial is at low RoB in all the domains.

Table 3. ERG assessment of trial quality using the NICE checklist

NICE checklist item	*CS Document B page 38*	ERG judgement	ERG rationale
Was randomisation carried out appropriately?	*Low RoB*	Low RoB	Kappos et al 2018[2] reports interactive response technology for generating randomisation numbers
Was the concealment of treatment allocation adequate?	*Low RoB*	Low RoB	Kappos et al 2018[2] reports interactive response technology for concealment of allocation
Were the groups similar at the outset of the study in terms of prognostic factors?	*Low RoB*	Low RoB	Kappos et al 2018[2] reports that baseline characteristics were similar between groups, (Table 1 Kappos et al 2018[2]); the CSR reports the baseline demographic characteristics in Table 11-2, page 97, MS disease history in Table 11-3 and other baseline characteristics in Table 11-4 and Table 11-5, and states that they were generally balanced across groups
Were the care providers, participants and outcome assessors blind to treatment allocation?	*Low RoB*	Low RoB	Care providers, participants, and outcome assessors were blind to treatment allocation. Kappos et al 2018[2] describes the trial as double-blind; the CSR, page 29 states that patients, investigator staff, persons performing the assessments, and data analysts remained blinded to the identity of the treatment from the time of randomisation until database lock of the Core Part. The identity of the treatments was concealed by the use of study drugs that were identical in packaging, labelling, schedule of administration, appearance, taste, and odor.
Were there any unexpected imbalances in drop-outs between groups?	*Low RoB*	Low RoB	There were no unexpected imbalance in study withdrawals. The reasons for all withdrawals were explained
Is there any evidence to suggest that the authors measured more outcomes than they reported?	*Low RoB*	Low RoB	There was no evidence to suggest that the authors measured more outcomes than they reported (all outcomes stated in the methods section were reported in the publication[2])
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	*Low RoB*	Low RoB	Intention-to-treat analysis was described in the CSR page 77. The primary analysis of the time to 3-month CDP used all available data from all patients in the FAS, irrespective of premature discontinuation from study medication and appropriate methods were used to account for missing data (CSR page 77: Patients who did not reach 3-month CDP during the study were censored at the latest date known to be at risk defined in the FAS as the date of the last EDSS assessment). Sensitivity analyses were also performed on the FAS, using 3 predefined assumptions for determination of confirmed progression

CDP = Confirmed disability progression; EDSS = Expanded disability status scale; FAS = Full analysis set; ITT = intent to treat; N/A = not applicable; RoB = risk of bias.

4.1.5 Evidence synthesis

Evidence synthesis for direct treatment comparisons was not applicable, since the SLR included only one study. Therefore, a narrative review was provided (CS Document B, B.2.2, page 23) of the single included trial which described the clinical effectiveness on siponimod.[2] The EXPAND[2] trial (ClinicalTrials.gov identifier: NCT01665144) is a phase III, multicentre, randomised, double-blind, parallel-group, placebo-controlled trial sponsored by the company, Novartis Pharmaceuticals. The trial was designed to investigate the use of siponimod compared to placebo in slowing disability progression in patients with SPMS.

4.1.5.1 Summary of the methods of review

As only one trial was included, no meta-analysis was conducted in the CS. The CS SLR identified 23 unique studies, of which 6 were eligible for inclusion in the analysis of indirect treatment comparison. See Section 4.3.1.1 for critique of the indirect comparisons.

4.2 Critique of trials of the technology of interest, their analysis and interpretation

Evidence for the clinical effectiveness on siponimod is presented from a single pivotal RCT EXPAND[2] which is described in detail in the CS (Document B, B.2.2 page 22-23). The CS provides summary information about the trial design, intervention, population, patient numbers (e.g., how many were eligible, randomised, allocated and dropped out), outcomes and statistical analyses. The EXPAND trial CSR was provided by the company for use within this appraisal. Neither the company nor the ERG identified any other relevant RCTs that meet the NICE decision problem.

The ERG compared the data extracted from Kappos et al (2018)[2] and the CSR with the information provided in CS Document B and the CS Appendices. The ERG considers the process of data extraction to be accurate with respect to the intervention and comparator in terms of the numbers of patients receiving drug and placebo, siponimod dose, and duration of treatment.

4.2.1 Study design

The EXPAND trial started on the 20th December 2012, the primary completion date was the 29th April 2016, and the estimated study completion date is the 22nd September 2023. The study duration was

described as up to 3 years or until the occurrence of a prespecified number (374) of CDP events (event-driven trial design).[2] The CS Document B presents the trial design in Figures 3 and 4 (page 143). Figure 4 is reproduced by the ERG in Figure 2. The ERG requested clarification regarding the event-driven trial design (A7). The company responded that "*EXPAND had a time-to-event end point. The timing of the primary analysis (i.e., analysis of the double-blind Core Part of the trial) was dependent on observing a pre-specific number of events*" in EXPAND (3-month CDP). Therefore, the design of EXPAND resulted in a variable treatment duration for patients, and lower patient numbers toward the end of the study (response A7). The ERG note that the Core Part of the trial was variable for each patient. The company state that the median exposure time was 18 months (response A7 and Figure 2), the ERG note that the actual time between the timepoint at which the last patient started their first dose of siponimod to the timepoint the last patient took their final treatment as part of the Core Part of the EXPAND was 11 months.

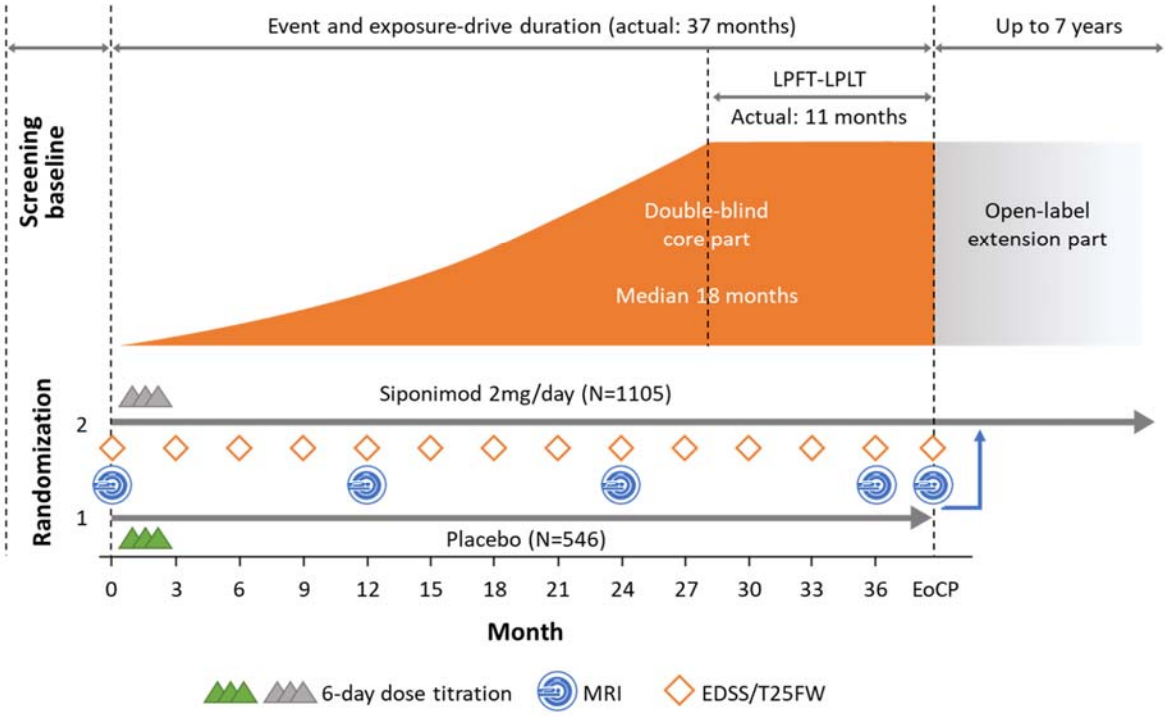


Figure 2. Study design and recruitment for EXPAND2 taken from CS Document B Figure 4 page 25

CS Document B page 25 *"The y-axis of the graph indicates the enrolment of patients. Dark grey indicates the recruitment and double-blind core part. Light grey indicates the open-label extension phase. From Feb 5, 2013 to June 2, 2015, 1,651 patients were randomised to the core part at 292 sites in 31 countries.* ***Abbreviations:*** *EDSS: Expanded Disability Status Scale; EoCP: end of core part; LPFT: last patient first treatment; LPLT: last patient last treatment; MRI: magnetic resonance imaging; T25FW: timed 25-foot walk.* ***Source:*** *Kappos et al. 2018.[2]"*

A flow chart of the participants in the EXPAND trial was presented in the CS Appendix D, page 142. Of the 1651 randomised patients in EXPAND, 1105 (67%) were assigned to the siponimod group (although 5 did not receive the study drug), and 546 (33%) were assigned to placebo.[2] In total, 319 patients withdrew from the trial: 197 in the siponimod group and 122 in the placebo group. The difference in withdrawal rates was significant (18% vs 22%, p=0.03). However, the ERG consider that the reasons for all withdrawals were explained adequately.

Detailed study design and methods used in the EXPAND trial are reported in CS Document B (Table 5, page 27), which accurately represent the data reported in the trial publication Kappos et al (2018)[2] and the CSR. The ERG note that Kappos et al (2018)[2] and the CSR state that the study was conducted in 292 hospital clinics and specialised MS centres in 31 countries, whereas CS Document B (Table 5, page 27) states the study was conducted 314 study locations in 31 countries.

4.2.1.1 Randomisation and blinding

Randomisation is described in CS Document B Table 5 (page 27). The randomisation ratio of EXPAND was 2:1 between the intervention and placebo arms, via Interactive Response Technology, and was stratified by region. Patients with 6-month CDP during double-blind treatment were reconsented to either continue double-blind treatment, switch to open-label siponimod, or stop study treatment while following an abbreviated schedule of assessments and either remain untreated or receive another DMT (see Section 4.2.7 for details of patient switching).

The EXPAND trial publication reported that siponimod and placebo were identical in packaging, labelling, schedule of administration, appearance, taste, and odour.[2] Patients and study staff remained masked to treatment assignment for the duration of the core part of the study. An independent doctor monitored patients during dose titration, and the counts for the total number of leucocytes, neutrophils, and lymphocytes were normally withheld by the central laboratory and only reported to the investigator in case of notable abnormalities.[2]

The ERG consider the processed of randomisation and blinding to be acceptable.

4.2.1.2 Dosage

The CS (Document B, Table 5, page 27-28) states that in the siponimod arm (n=1,105), siponimod 2 mg was given once daily orally, and in the placebo arm (n=546), placebo was given once daily orally. Siponimod was titrated from 0.25 mg to the 2 mg maintenance dose for days 1-6 (Day 1 and 2: 0.25 mg; Day 3: 0.5 mg; Day 4: 0.75 mg; Day 5: 1.25 mg). The titration regimen for initial treatment was reported accurately in the CS when compared to Table 9-1 of the CSR (page 26). The CS (Document B, Table 5 page 27-28) states that re-titration was recommended if treatment was interrupted for four or more consecutive days. However, the ERG note that the CSR additionally states that re-titration was also required for patients who missed one dose or more during dose titration.

4.2.1.3 Key eligibility criteria

Key inclusion criteria are reported in CS Document B Table 4 (page 26) including; age 18-60 years, diagnosis of SPMS, documented EDSS score of 3.0-6.5 at screening, history of RRMS, documented EDSS progression in the two years before the study, and no evidence of relapse in the 3 months before randomisation. Key exclusion criteria included substantial immunological, cardiac, or pulmonary conditions, ongoing macular oedema, uncontrolled diabetes, CYP2C9*3*3 genotype, and varicella zoster virus antibody negative status. The ERG considers these inclusion/exclusive appropriate.

Of the [redacted] patients screened, the CSR (page 84) reports [redacted] failed screening prior to randomisation, of whom [redacted] were classified as ineligible based on inclusion/exclusion criteria. The most common inclusion criterion leading to screen failure was absence of documented EDSS progression in medical history as required by the protocol [redacted] The most common exclusion criteria [redacted] leading to screen failure were: abnormal laboratory values [redacted], positive serology for hepatitis antigens [redacted], disease/condition that could have interfered with study participation [redacted], and prohibited medications [redacted]. The ERG note that >20% screen failures may reduce the generalisability of the findings, although the study publication states that the trial "*included a typical SPMS population, with characteristics compatible with natural history data and with other studies in SPMS*".[2]

The CS reported the full eligibility criteria in CS, Appendix L.

4.2.1.4 Study participants and baseline characteristics

A summary of the EXPAND patient baseline characteristics was reported in CS Document B (Table 6, page 34) which accurately represent the data reported in Kappos et al (2018)[2] and the CSR.

The baseline characteristics of patients randomised in the EXPAND trial are reproduced in ERG Table 4. The ERG assessed the difference between the intervention and control groups for the categorical variables, but not for the continuous variables due to lack of data. We found no statistically significant differences between the siponimod and placebo groups for the categorical variables at the 5% significance level.

Table 4. Summary of EXPAND2 trial patient baseline characteristics, replicated from CS Document B Table 6, page 34.

Demographic variable	Siponimod N=1,105	Placebo N=546
Age groups – n (%)		
18–40	188 (17)	103 (19)
>40	917 (83)	443 (81)
Age (years)		
Mean (SD)	48.0 (7.8)	48.1 (7.9)
Median	49.0	49.0
Min – Max	22–61	21–61
Sex – n (%)		
Female	669 (61)	323 (59)
Male	436 (39)	223 (41)
Duration of MS since diagnosis (years)		
Mean (SD)	12.9 (7.9)	12.1 (7.5)
Median	12.0	11.2
Min – Max	0.1–44.4	0.4–39.4
Duration of MS since first symptom (years)		
Mean (SD)	17.1 (8.4)	16.2 (8.2)
Median	16.4	15.4
Min – Max	1.4–45.0	1.3–43.0
Time since conversion to SPMS (years)		
Mean (SD)	3.9 (3.6)	3.6 (3.3)
Median	2.6	2.5
Min – Max	0.1–24.2	0.1–21.7
Number of relapses in the last 2 years prior to screening		
Mean (SD)	0.7 (1.2)	0.7 (1.2)
Median	0.0	0.0
Min – Max	0–12	0–8
Number of relapses in the last 2 years prior to screening (categories) – n (%)		
None	712 (64)	343 (63)

Demographic variable	Siponimod N=1,105	Placebo N=546
Number of relapses in the last year prior to screening		
Mean (SD)	0.2 (0.5)	0.3 (0.6)
Median	0.0	0.0
Min – Max	0–4	0–4
Number of relapses in the last year prior to screening (categories) – n (%)		
None	878 (79)	416 (76)
EDSS		
Mean (SD)	5.4 (1.1)	5.4 (1.0)
Median	6.00	6.00
Min – Max	2.0–7.0	2.5–7.0
EDSS (categories) – n (%)		
<3.0	6 (1)	2 (<1)
3.0–4.5	312 (28)	148 (27)
5.0–5.5	165 (15)	100 (18)
6.0–6.5	620 (56)	295 (54)
>6.5	2 (<1)	1 (<1)
Number of Gd-enhancing T1 lesions (categories) – n (%)		
0	833 (75)	415 (76)
≥1	237 (21)	114 (21)
Not assessed	35 (3)	17 (3)
Volume of T2 lesions (mm3)		
Mean (SD)	15,632 (16,268)	14,694 (15,620)
Median	10,286	9,994
Min – Max	23–116,664	0–103,560
Normalised brain volume (cc)		
Mean (SD)	1,422 (86)	1,425 (88)
Median	1,421	1,425
Min – Max	1,136–1,723	1,199–1,691
MS DMTs (Approved for the treatment of MS)		
Any MS DMT	860 (78)	432 (79)
No previous use	245 (22)	114 (21)

9-HPT: nine-hole peg test; DMT: disease-modifying therapy; EDSS: Expanded Disability Status Scale; MS: multiple sclerosis; MSSS: multiple sclerosis severity scale; SD: standard deviation; SDMT: symbol digit modalities test; SPMS: secondary progressive multiple sclerosis; T25FW: timed 25-foot walk test. (Kappos et al. 2018.[2])

The ERG note that patients randomised to siponimod had similar mean exposure to double-blind study drug ([redacted]) compared with placebo ([redacted]). Acknowledging the 2:1 randomisation ratio, cumulative exposure to siponimod was [redacted] patient-years versus [redacted] patient-years in placebo. Most patients in each group (80.4% siponimod, 78.8% placebo) had at least 12 months of exposure to double-blind study drug (see Section 4.2.1); however, less than 30% of patients in either group had at least 24

months of exposure, this was due to the event-driven study design leading to variable exposure duration for different patients.

Mean exposure to open-label siponimod was [redacted] months for the [redacted] patients initially randomised to siponimod and [redacted] months for the [redacted] patients who switched to open-label siponimod from placebo at 6-month CDP. Patient-years of exposure to open-label siponimod were [redacted] in the siponimod group and [redacted] in the patients who switched from placebo.

EXPAND was conducted in 31 countries across 314 study locations (CS Document B Table 5, page 27). The CS Document B (page 90) states that 10 investigation sites were in the UK. However, the ERG cannot confirm the number of patients who were enrolled from the UK sites, as this information was not reported in the CS documents or the CSR. The company states that the results of the EXPAND trial can be generalised to the UK population as "*the majority of the study population were* [redacted] *which is in line with the majority White population in the UK (86.0%)"* (CS Document B page 90). However, the ERG do not consider this sufficient satisfactory evidence of generalisability and suggests that there is potential variation geographically (across the 31 countries) in outcomes and potentially in accompanying clinical practice, in treatment physiotherapy and in standard of care regimes.

4.2.1.5 Outcomes

The outcomes reported in the CS for EXPAND generally matched the NICE final scope (see Section 3.4). The NICE final scope lists the specified outcomes as:

- Disability (for example, expanded disability status scale [EDSS])
- Disease progression
- Relapse rate and severity (for those with active disease)
- Symptoms of multiple sclerosis such as fatigue, cognition and visual disturbance
- MRI parameters (for example, lesion counts and brain volume change)
- Freedom from disease activity
- Mortality
- Adverse effects of treatment
- Health-related quality of life (HRQoL).

The CS provides a list of the primary and some secondary efficacy outcomes in CS Document B, Table 3, page 23. The ERG conducted a comparison of outcomes specified in the CS and those reported in the

CSR and Kappos et al (2018)[2] which is provided in Table 5. The outcomes specified in the CS appear appropriate and in line with other NICE appraisals of this type.[19]

In the EXPAND[2] trial, disability progression was assessed using the EDSS. The primary endpoint of EXPAND was the "*time to 3-month CDP. CDP was defined as a 1-point increase in EDSS if the baseline score was 3.0-5.0 or a 0.5 increase if the baseline score was 5.5-6.5"* (CS Document B, Table 3, page 23).

The CS reports the key secondary endpoints as including "*time to 3-month confirmed worsening of at least 20% from baseline in T25FW, and change from baseline in T2 lesion volume."* Additional secondary endpoints included: time to 6-month CDP as measured by the EDSS, reducing frequency of confirmed relapses (including ARR) and HRQoL. MS relapse was defined as appearance of a new neurological abnormality or worsening of previously stable or improving pre-existing neurological abnormality, separated by at least 30 days from onset of a preceding clinical demyelinating event. Additionally, the abnormality must have been present for at least 24 hours and occurred in the absence of fever (<37.5°C) or known infection.

Table 5 Comparison of outcomes specified in the CS and reported in the CSR and Kappos et al (2018)2

Outcomes reported in the CSR and Kappos et al (2018)[2]	Reported in the CS
Primary outcomes	
Time to 3-month CDP	Yes
Key secondary outcomes	
Time to 3-month confirmed worsening of at least 20% from baseline in T25W	Yes
Increase in T2 lesion volume from baseline	Yes
Additional secondary outcomes	
Time to 6-month CDP as measured by EDSS	Yes
Frequency of confirmed relapses as evaluated by the ARR; time to first relapse; proportion of relapse-free patients	Yes
Patient reported outcome: MSWS-12	Yes
Inflammatory disease activity and burden of disease, as measured by conventional MRI: T1 Gd-enhancing lesions, new or enlarging T2 lesions, brain volume	Yes
Efficacy of siponimod relative to placebo on 3-month CDP as measured by EDSS in the following subgroups: • SPMS patients with or without superimposed relapses • Rapidly evolving patients, defined as ≥1.5 point EDSS change in the 2 years prior to study start, and in those not meeting this criteria	Yes

• Patients with moderate and severe disease course, as defined MSSS of 4 or more at baseline, and in those not meeting this criteria	
Safety and tolerability	Yes
Outcomes reported in the CSR only	
Exploratory outcomes	
HRQoL as measured by the MSIS-29 and EQ-5D	Yes MSIS-29 and EQ-5D: CS (p51)
Defined cognitive tests: • PASAT • SDMT • BVMT-R	Yes SDMT: CS (p51) PASAT and BVMT-R: Appendix L
MSFC z-score	Yes Appendix L
Low contrast visual acuity	Yes Appendix L
Evolution of acute lesions into chronic black holes by MRI (CSR page 128): • Number of new T1 hypointense lesions that were T1 Gd-enhancing in previous scheduled scan • Proportion of patients with T1 Gd-enhancing lesions evolving to T1 hypointense lesions • Proportion of T1 Gd-enhancing lesions evolving to T1 hypointense lesions	No
Endpoints listed in methods of CSR but no results reported	
Time to: • 3-month confirmed worsening of ≥20% from baseline in the T25W or • 3-month CDP as measured by EDSS score or • 3-month confirmed worsening of ≥20% from baseline in the 9-HPT in either one of the hands (dominant or non-dominant). Reported as an outcome but no results given in the CSR	NA
Clinically relevant responder subgroups. Reported as an outcome but no results given in the CSR	NA
Relationship between disability progression endpoints and selected safety parameters and drug concentration/lymphocyte count. Reported as an outcome but no results given in the CSR	NA
PK of siponimod. Reported as an outcome but no results given in the CSR	NA
Effects of siponimod compared to placebo on 3-month CDP as measured by EDSS in the following subgroups: • Patients previously treated, or not, with interferon beta-1b • Treatment-naive and patients with prior treatment with disease-modifying drugs. Reported as an outcome but no results given in the CSR	NA

BVMT-R=Brief visuospatial memory test-revised; CDP=confirmed disability progression; EDSS= Expanded disability status scale; EQ-5D=European quality of life 5-dimensions; gd=gadolinium; 9-HPT=9-Hole Peg Test; HRQoL= Health-related quality of life; MRI= magnetic resonance imaging; MSFC= multiple sclerosis functional composite; MSIS-29=Multiple sclerosis impact scale; MSSS= Multiple sclerosis severity scale; MSWS= Multiple sclerosis walking scale; NA=not applicable; PASAT=Paced auditory serial addition test; PK= pharmacokinetics; SDMT=Symbol digit modalities test; SPMS= Secondary progressive multiple sclerosis; T25W= Timed 25-foot walk test

The ERG consider the company's interpretation of outcome data and effectiveness to be appropriate, but we are unclear why they have not reported data for all outcomes included in the CSR (as described in Table 5).

4.2.1.6 Description and critique of the company's approach to trial statistics

The company's approach to trial statistics is presented in the CS section B.2.4 (page 36).

The hypothesis was tested using stratified log-rank tests, and an adjusted Cox proportional hazards (PH) model which provided the hazard ratio estimates. The ERG consider this suitable for the design of the trial.

The ERG reproduced a similar sample size calculation to that presented in Table 7 of the CS Document B (page 37) and are satisfied that the trial was suitably powered to detect the specified difference in the primary outcome (HR of 0.70 in 3-month CDP).

The results presented by the company came from analyses specified in the amended protocol, stopping the Core Part of the study when 374 patients with 3-months CDP had been observed to approximately three years after randomisation of the first patient and at least 374 patients (result of the sample size calculation) with 3-month CDP had been observed.

For the primary outcome (3-month CDP), the company adjusted the significance level so that the null hypothesis was to be rejected for the between-group comparison if the observed p-value was less than 0.0434, according to the O'Brien-Fleming alpha correction. The ERG considers this an appropriate method of adjusting for multiple comparisons, however the calculation of the 0.0434 significance level was not reported. Furthermore, there was no mention on adjusting for multiple comparisons for key secondary endpoints.

The log-rank test was stratified by country, baseline EDSS and SPMS group (with or without superimposed relapses at baseline). The estimated HR was estimated with 95% Wald CI, from which the risk reduction was calculated as (1 – HR) x 100.

The EXPAND[2] study protocol was amended on 6th October 2015, to update the criterion for stopping the Core Part of the study from when 374 patients with 3-month CDP had been observed, to approximately three years after randomisation of the first patient and at least 374 patients with 3-month CDP had been observed. This was because more 3-month CDP events occurred than expected at the planning stage of the study, which would have led to an estimated study duration of 33 months as opposed to 42 months which was originally planned. Study enrolment was also lower than anticipated. Therefore, without the amendment, around 300 patients would be treated for at least 24 months in a placebo-controlled setting, whereas in the original protocol this was assumed for the majority of patients.

Treatment allocation was performed using interactive response technology, and participants and care providers were blinded. This was deemed suitable by the ERG (see Section 4.1.4).

4.2.1.7 Planned subgroup analyses

The planned subgroup analyses are described in CS Document B (Table 5, page 32) and CS Appendix E (page 144). The ERG confirm that they are consistent with the CSR (page 123). The subgroups of patients were defined in the CS as:

- Baseline demographic factors and treatment history (gender, previous interferon β-1b treatment, previous MS DMT treatment, [previous interferon β was added as a *post-hoc* analysis])
- Baseline disease characteristics:
    - Patients with SPMS or without superimposed relapses in the 2 years prior to the screening visit
    - Rapidly evolving patients (defined based on historical EDSS scores i.e., with an EDSS change ≥1.5 in the 2 years prior to or at study start). All patients who were adjudicated for disability progression were not assigned to the rapidly evolving patient subgroup
    - Disease course: patients with Global MSSS ≥4 were included in the moderate/severe subgroup
    - Number of T1 Gd-enhancing lesions at baseline (0; ≥1)
- Patients with or without at least one confirmed relapse at any time on or after Day 1.

The CS states that subgroup analyses were performed to "*examine whether the treatment difference was consistent in patients with different demographic/baseline or post-treatment disease characteristics*" (CS Document B page 32).

4.2.2 Primary and secondary results for EXPAND[2]

The ERG has summarised and critiqued the effectiveness results from the EXPAND trial as reported in the CS Section B.2.6, page 39-55 and in Kappos et al (2018).[2] The results of EXPAND have been reproduced by the ERG in Tables 6 to Table 10 for completeness.

4.2.3 Primary outcome: Confirmed Disability Progression 3 months

The risk of 3-month CDP, assessed via EDSS, was significantly lower in the siponimod group compared to the placebo group (HR =0.79, 95% CI: 0.65, 0.95). The ERG has summarised the CDP endpoints in Table 6.

4.2.4 Secondary outcome: Confirmed Disability Progression 6 months

Time to 6-month CDP (as measured by the EDSS) was a secondary outcome; the risk of 6-month CDP was significantly lower in the siponimod group compared to the placebo group (HR 0.74, 95% CI: 0.60 to 0.92; p = 0.0058) (Table 6).

The ERG note that results were robust to sensitivity analyses conducted by the company; as reported in Section B.2.6.7 of the CS, page 52. The estimates provided in the sensitivity analysis were very close to the estimates of the main analysis. However, the confidence intervals were much wider and out of the six estimates provided only one was significant (CS Document B, page 54).

Table 6. CDP outcomes reported in EXPAND

	Siponimod	Placebo
Number of patients	1105	546
Time to 3-month CDP (primary endpoint)		
Number of progressions (%)	288 (26.3)	173 (31.7)
HR for progression (95% CI)	0.79 (0.65, 0.95)	
p-value	0.0134	
Time to 6-month CDP (secondary endpoint)		
Number of progressions (%)	218 (19.9)	139 (25.5)
HR for progression (95% CI)	0.74 (0.60, 0.92)	
p-value	0.0058	

CDP = Confirmed Disability Progression; CI = confidence interval

4.2.5 Secondary outcomes: functional measures, MRI activity and relapses

4.2.5.1 Functional outcomes

The ERG have summarised the functional outcome measures in Table 7. The proportion of patients reaching 3-month confirmed worsening in T25FW was not significantly reduced in the siponimod group compared to the placebo group (HR 0.94, 95% CI: 0.80 to 1.10; p = 0.4398). The change from baseline MSWS-12 converted score at 12 months was not significantly reduced in the siponimod group compared to the placebo group (mean difference -1.83, 95% CI: -3.85 to 0.19; p = 0.0764). At 24 months (MSWS-24), the mean difference between the siponimod and placebo groups was also not statically significant (mean difference -1.23, 95% CI: -3.89 to 1.44; p = 0.3671).

Table 7 Functional outcome measures

	Siponimod	Placebo
Number of patients	1105	546
3-months confirmed worsening in T25FW		
Number of progressions (%)	432 (39.7)	225 (41.4)
HR for progression (95% CI)	0.94 (0.80, 1.10)	
p-value	0.4398	
MSWS-12 (Month 12)		
Mean change from baseline (SE)	1.53 (0.678)	3.36 (0.908)
Mean difference Sip-placebo (95% CI)	-1.83 (-3.85, 0.19)	
p-value	0.0764	
MSWS-12 (Month 24)		
Mean change from baseline (SE)	4.16 (0.848)	5.38 (1.167)
Mean difference Sip-placebo (95% CI)	-1.23 (-3.89, 1.44)	
p-value	0.3671	

T25FW = Times 25-foot Walk Test; MSWS-12 = Multiple Sclerosis Walking Test

4.2.5.2 MRI activity outcomes

The CS reports a range of MRI activity outcomes which the ERG have summarised in Table 8. The change from baseline T2 lesion volume at 12 months was significantly [redacted] in the siponimod group compared to the placebo group (mean difference [redacted], 95% CI: [redacted] to [redacted]; p = [redacted]). At 24 months, the mean difference between the siponimod and placebo groups was [redacted] (mean difference [redacted], 95% CI: [redacted] to [redacted]; p [redacted]). Thus, the overall mean difference between the siponimod and placebo groups across months 12 and 24 was also statistically significant (mean difference -695.3, 95% CI: -877.3 to -513.3; p < 0.0001).

The proportion of patients free of T1 Gd-enhancing lesions was [redacted] in the siponimod group compared to the placebo group: at 12 months post-baseline ([redacted] vs [redacted]); at 24 months ([redacted] vs [redacted]); and for all post-baseline scans (89.4% vs 66.9%). However, the ERG note that no formal statistical tests were performed to test the difference in proportions between the two groups.

At 12 months, the adjusted mean T1 Gd-enhancing lesions per patient per scan was significantly [redacted] in the siponimod group compared to the placebo group (rate ratio [redacted]; 95% confidence interval: [redacted] to [redacted]; p [redacted]X). At 24 months, the adjusted mean T1 Gd-enhancing lesions per patient per scan was also significantly lower in the siponimod group compared to the placebo group (rate ratio [redacted]; 95%

confidence interval: [redacted] to [redacted]; p [redacted]). The adjusted mean T1 Gd-enhancing lesions per patient per scan, for all post-baseline scans, was significantly lower in the siponimod group compared to the placebo group (rate ratio 0.14; 95% CI: 0.10 to 0.19; p < 0.0001).

The proportion of patients free of new or newly enlarging T2 lesions was significantly [redacted] in the siponimod group compared to the placebo group: at 12 months post-baseline ([redacted] vs [redacted]); at 24 months ([redacted] vs [redacted]); and for all post-baseline scans (56.9% vs 37.3%). No formal statistical tests were performed to test the difference in proportions between the two groups.

At 12 months, the adjusted mean of new or newly enlarging T2 lesions was significantly [redacted] in the siponimod group compared to the placebo group (rate ratio: [redacted]; 95% CI: [redacted] to [redacted]; p [redacted]). At 24 months, the adjusted of mean new or newly enlarging T2 lesions was also significantly [redacted] in the siponimod group compared to the placebo group (rate ratio: [redacted]; 95% CI: [redacted] to [redacted]; p [redacted]).

The adjusted mean of new or newly enlarging T2 lesions, for all post-baseline scans, was significantly lower in the siponimod group compared to the placebo group (rate ratio 0.19; 95% CI: 0.16 to 0.24; p < 0.0001).

The change from baseline of percentage brain volume was significantly reduced in the siponimod group compared to the placebo group: at 12 months post-baseline (rate reduction 0.175; 95% CI: 0.103 to 0.247; p < 0.0001); at 24 months (rate reduction 0.128; 95% CI: 0.021 to 0.236; p < 0.0001); and for the average over months 12 and 24 (rate reduction 0.15; 95% CI: 0.07 to 0.23; p < 0.0001).

Table 8 MRI activity outcomes

	Siponimod	**Placebo**
	1105	546
T2 lesion volume (Month 12)		
Mean change from baseline (SE)	[redacted]	[redacted]
Mean difference Sip-placebo (95% CI)	[redacted]	
p-value	[redacted]	
T2 lesion volume (Month 24)		
Mean change from baseline (SE)	[redacted]	[redacted]
Mean difference Sip-placebo (95% CI)	[redacted]	
p-value	[redacted]	
T2 lesion volume (Average over Months 12 and 24)		

	Siponimod	Placebo
	1105	546
Mean change from baseline (SE)	183.9 (66.33)	879.2 (85.43)
Mean difference Sip-placebo (95% CI)	-695.3 (-877.3, -513.3)	
p-value	< 0.0001	
T1 Gd-enhancing lesions (Month 12)		
Proportion of patients free of T1 Gd-enchaning lesions (%)	[redacted]	[redacted]
Mean difference Sip-placebo (95% CI)	NA	
p-value	NA	
T1 Gd-enhancing lesions (Month 24)		
Proportion of patients free of T1 Gd-enchaning lesions (%)	[redacted]	[redacted]
Mean difference Sip-placebo (95% CI)	NA	
p-value	NA	
T1 Gd-echancing lesions (All post-baseline scans)		
Proportion of patients free of T1 Gd-enchaning lesions (%)	917 (89.4)	341 (66.9)
Mean difference Sip-placebo (95% CI)	NA	
p-value	NA	
T1 Gd-enhancing lesions per patient per scan (Month 12)		
Mean (95% CI)	[redacted]	[redacted]
Rate ratio (95% CI)	[redacted]	
p-value	[redacted]	
T1 Gd-enhancing lesions per patient per scan (Month 24)		
Mean (95% CI)	[redacted]	[redacted]
Rate ratio (95% CI)	[redacted]	
p-value	[redacted]	
T1 Gd-enhancing lesions per patient per scan (All post-baseline scans)		
Mean (95% CI)	0.08 (0.07, 0.10)	0.60 (0.47, 0.76)
Rate ratio (95% CI)	0.14 (0.10, 0.19)	
p-value	< 0.0001	
New or newly enlarging T2 lesions (Month 12)		
Proportion of patients free of new or newly enlarging lesions (%)	[redacted]	[redacted]
Mean difference Sip-placebo (95% CI)	NA	
p-value	NA	
New or newly enlarging T2 lesions (Month 24)		
Proportion of patients free of new or newly enlarging lesions (%)	[redacted]	[redacted]
Mean difference Sip-placebo (95% CI)	NA	
p-value	NA	
New or newly enlarging T2 lesions (All post-baseline scans)		
Proportion of patients free of new or newly enlarging lesions (%)	584 (56.9)	190 (37.3)
Mean difference Sip-placebo (95% CI)	NA	

	Siponimod	Placebo
	1105	546
p-value	NA	
New or enlarging T2 lesions (Month 12)		
Mean (95% CI)	[redacted]	[redacted]
Rate ratio (95% CI)	[redacted]	
p-value	[redacted]	
New or enlarging T2 lesions (Month 24)		
Mean (95% CI)	[redacted]	[redacted]
Rate ratio (95% CI)	[redacted]	
p-value	[redacted]	
New or enlarging T2 lesions (All post-baseline scans)		
Mean (95% CI)	0.70 (0.58, 0.84)	3.60 (3.03, 4.29)
Rate ratio (95% CI)	0.19 (0.16, 0.24)	
p-value	< 0.0001	
Percentage Brain Volume Change (Month 12)		
Mean change from baseline (SE)	-0.283 (0.0264)	-0.458 (0.0341)
Rate reduction (95% CI)	0.175 (0.103, 0.247)	
p-value	< 0.0001	
Percentage Brain Volume Change (Month 24)		
Mean change from baseline (SE)	-0.711 (0.0356)	-0.839 (0.0476)
Rate reduction (95% CI)	0.128 (0.021, 0.236)	
p-value	0.0196	
Percentage Brain Volume Change (Average over Months 12 and 24)		
Mean change from baseline (95% CI)	-0.50 (-0.55, -0.44)	-0.65 (-0.72, -0.58)
Rate reduction (95% CI)	0.15 (0.07, 0.23)	
p-value	0.0002	

4.2.5.3 Relapse-related outcomes

The CS reported relapse-related outcomes in the CS (Document B), reproduced in Table 9. The key outcomes were ARR and time to first confirmed relapse. The adjusted ARR for confirmed relapses was significantly lower in the siponimod group compared to the placebo group (ARR ratio: 0.445; 95% CI: 0.337 to 0.587; p<0.0001). The time to first confirmed relapse showed a significant risk reduction in the favour of the siponimod group compared to the placebo group (HR: 0.54; 95% CI: 0.41 to 0.70; p<0.0001).

A lower proportion of patients experienced any relapse or a confirmed relapse in the siponimod group compared to the placebo group. The appropriate statistical tests were not reported in the CS and the ERG were unable to assess the information without the IPD from the EXPAND[2] trial.

Table 9 Relapse-related outcome measures

	Siponimod	Placebo
	1105	546
Annualised Relapse Rate (ARR) for confirmed relapses		
Adjusted ARR (95% CI)	0.071 (0.055, 0.092)	0.160 (0.123, 0.207)
ARR ratio (95% CI)	0.445 (0.337, 0.587)	
p-value	< 0.0001	
Time to first confirmed relapse		
Number with events (%)	113 (10.7)	100 (18.9)
HR (95% CI)	0.54 (0.41, 0.70)	
p-value	< 0.0001	
Proportion of patients with relapse (any relapse)		
Number with events (%)	[redacted]	[redacted]
HR (95% CI)	NA	
p-value	NA	
Proportion of patients with relapse (confirmed relapse only)		
Number with events (%)	[redacted]	[redacted]
HR (95% CI)	NA	
p-value	Na	

4.2.5.4 Patient reported outcomes

The CS reported outcomes for MSIS-29 and EQ-5D-3L. The ERG have summarised the average values (individual readings were taken every 6, 12, 18 and 24 months) in Table 10.

Overall change from baseline of the MSIS-29 physical impact scores was significantly [redacted] in the siponimod group compared to the placebo group (mean difference: [redacted]; 95% CI: [redacted] to [redacted]; p = [redacted]). It was also significantly [redacted] for the siponimod group during months 12 and 18.

The overall change from baseline of the MSIS-29 psychological impact scores was significantly [redacted] in the siponimod group compared to the placebo group (mean difference: [redacted]; 95% CI: [redacted] to [redacted]; p = [redacted]). It was not significantly [redacted] for the siponimod group during any of the measurements at 6, 12, 18 or 24 months.

For the EQ-5D-3L health state, the overall change from baseline was significantly [redacted] in the siponimod group compared to the placebo group (mean difference: [redacted]; 95% CI: [redacted] to [redacted]; p = [redacted]). It was also significantly [redacted] for the siponimod group during month 12 only, and not for month 24. Finally, the overall change from baseline of the EQ-5D visual analogue scale (VAS) was not significantly [redacted] in the siponimod group compared to the placebo group (mean difference: [redacted]; 95% CI: [redacted] to [redacted]; p = [redacted]).

Table 10 Patient reported outcomes

	Siponimod	**Placebo**
	1105	546
Multiple Sclerosis Impact Scale (MSIS-29): Physical Impact		
Mean change from baseline (SE) overall all visits	[redacted]	[redacted]
Mean difference (95% CI)	[redacted]	
p-value	[redacted]	
Multiple Sclerosis Impact Scale (MSIS-29): Psychological Impact		
Mean change from baseline (SE) overall all visits	[redacted]	[redacted]
Mean difference (95% CI)	[redacted]	
p-value	[redacted]	
EQ-5D-3L		
Mean change from baseline (SE) overall all visits	[redacted]	[redacted]
Mean difference (95% CI)	[redacted]	
p-value	[redacted]	
EQ-5D Visual Analogue Scale (VAS)		
Mean change from baseline (SE) overall all visits	[redacted]	[redacted]
Mean difference (95% CI)	[redacted]	
p-value	[redacted]	

4.2.6 Subgroup analyses

The company presented a number of analyses by predefined subgroups for the primary endpoint in the CS Document B page 57. The subgroups were:

- Patients with SPMS with or without superimposed relapses
- Patients with or without rapidly evolving disease
- Patients with multiple sclerosis severity scale (MSSS) score ≥ 4 (moderate or severe disease course) and MSSS < 4 at baseline

The company also conducted additional analysis of time to 3-month CDP on the following baseline characteristics:

- Previous interferon β-1b treatment
- Previous MS DMT treatment
- Number of baseline T1 Gd-enhancing lesions
- Baseline EDSS score
- Duration of MS since first symptoms
- Demographic characteristics (gender and age)

Additional subgroup analyses were conducted for the following endpoints:

- Time to 3-month confirmed worsening in T25FW of at least 20%
- Change from baseline in T2 lesion volume
- Time to 6-month CDP
- ARR

The company produced a forest plot of time to 3-month CDP for these subgroups (excluding additional subgroups not specific to the primary endpoint) (CS Appendix E, Table 62, page 144). Results based on these pre-defined subgroups did not identify any subgroups more or less likely to benefit significantly from siponimod. As the confidence intervals of each subgroup crosses the line of the overall treatment effect, there were no significant treatment interactions by subgroup.

However, the company state that "*the study was not designed to test for a statistically significant difference between siponimod and placebo in these subgroups. The study was also not designed to test for the consistency of the treatment effect across subgroups*"(CS Document B page 57).

4.2.6.1 Active SPMS subgroup

The CS provided a specific subgroup analysis for the population of active SPMS (see Table 11). Active SPMS was defined by the company as ongoing relapses and/or MRI activity in patients with SPMS (CS Document B, page 58). However, the ERG note the company's statement in the decision problem that there are *"difficulties in accurately defining a patient as non-Active*" (CS Document B, Table 1, page 12) and the company response to clarification question A3 and A21d that "*it is not possible to define a*

subgroup a priori with 100% certainty, resulting in inaccurate or uninterpretable efficacy results for a Non-Active SPMS subgroup population."

In response to clarification question A21d regarding any potential beneficial effects for CDP in non-active subgroups, the company stated that "*due to relapses acting as an intercurrent event when undertaking CDP analysis and due to the impossibility of defining a priori whether any given patient has a Non-Active phenotype, the estimands analysis is to be considered the best approach for determining the relative efficacy of siponimod on CDP vs placebo unaffected by relapses. This sensitivity analysis gave results consistent with the effect on the overall population for 3-month CDP (RR [redacted] vs. HR 0.79) and 6-month CDP (RR [redacted] vs. HR 0.74). The consistency of these results is indicative that most, if not all, of the effect of siponimod on disability progression is independent of relapses, meaning patients treated with siponimod benefit from the effect of treatment on disability progression irrespective of their relapsing/activity status*".

The ERG note that indirect treatment comparisons between siponimod and other DMTs were not presented by the company for both active or non-active subgroups. The company state that there was a "*lack of data available to inform the comparisons, as described for the active subgroup in CS Document B Section B.2.9.3, Pages 72–74*". The ERG note that this section refers to a feasibility assessment of the active SPMS subgroup. The CS Document B Table 39 (page 72) presents the non-reported/non-comparable data for two trials (NA study and ASCEND) and differences in the remaining three studies in active subgroup populations which the company suggests "*a MAIC focussing on active SPMS specifically is not possible*" (clarification response A21d).

Base line characteristics: active subgroup

A *post hoc* active SPMS subgroup population from the EXPAND trial was presented in the CS due to uncertainty as to the final licensed population for siponimod. In the EXPAND trial, the *post hoc* active SPMS subgroup included patients who experienced relapses in the two years prior to the study and/or who had gadolinium-enhanced T1 lesions at baseline.[2] The baseline characteristics of this subgroup are presented in Table 25 of the CS Document B (page 59) and in section E.2.1 in the CS appendices (page 145).

A total of [redacted] (47.2% of the full analysis set [FAS]) out of 1651 patients made up the active SPMS subgroup ([redacted] in siponimod, [redacted] in placebo). This was consistent with the 2:1 randomisation of the overall trial. [redacted] patients of the 1099 randomised to the siponimod group in the FAS and [redacted] of the 546 patients randomised to the placebo group in the FAS could not be classified as either active of non-active due to missing baseline characteristics for either relapse history or MRI (clarification response A4). This CS did not provide information as to why the baseline information was missing or how they handled missing data in the analysis (e.g., conducting a sensitivity analysis by multiple imputation).

The ERG compared the active SPMS population to the ITT population from EXPAND. The numbers appear to be similar through visual inspection, however, the ERG would need to make a formal assessment of the EXPAND IPD to confirm that the ITT population could potentially act as a proxy for the active SPMS population. However, the ERG emphasise that the efficacy estimates from the subgroup populations were not planned in the design of the EXPAND trial, and the subgroup of active SPMS patients are not what is included in the anticipated licence for siponimod (clarification response A3). Given the evidence we have, the ERG consider the active SPMS population to be comparable to the ITT population. However, without access to the IPD we are unable to make a formal assessment.

In the active SPMS subgroup, the risk of 3-month CDP and 6-month CDP was significantly [redacted] in the siponimod group compared to the placebo group (HR: [redacted], 95% confidence interval: [redacted] to [redacted]; p = [redacted]) (HR [redacted], 95% CI: [redacted] to [redacted]; p = [redacted]).

The adjusted ARR for confirmed relapses was significantly [redacted] in the siponimod group compared to the placebo group (ARR ratio: [redacted]; 95% CI: [redacted] to [redacted]; p = [redacted]).

The time to first confirmed relapse showed a significant risk reduction [redacted] of the siponimod group compared to the placebo group (HR: [redacted]; 95% CI: [redacted]to [redacted]; p = [redacted]). The ERG note the significantly [redacted] endpoints for the *post hoc* active SPMS subgroup. The effect of siponimod on disability progression (time to 3-month CDP) in patients with non-relapsing (non-active) SPMS subgroup was [redacted]([redacted]). Therefore, there is uncertainty if siponimod is effective in the non-active subgroup of patients

Table 11. Primary and secondary endpoints for the active SPMS subgroup

	Siponimod	Placebo
	[redacted]	[redacted]
Time to 3-month CDP (primary endpoint)		
Number of progressions (%)	[redacted]	[redacted]
HR for progression (95% CI)	[redacted]	
p-value	[redacted]	
Time to 6-month CDP (secondary endpoint)		
Number of progressions (%)	[redacted]	[redacted]
HR for progression (95% CI)	[redacted]	
p-value	[redacted]	
Annualised Relapse Rate (ARR) for confirmed relapses		
Adjusted ARR (95% CI)	[redacted]	[redacted]
ARR ratio (95% CI)	[redacted]	
p-value	[redacted]	
Time to first confirmed relapse		
Number with events (%)	[redacted]	[redacted]
HR (95% CI)	[redacted]	
p-value	[redacted]	

4.2.7 Safety (adverse events)

- The CS (Document B, page 79) state that the "safety of siponimod was evaluated through the assessment of treatment-emergent adverse events (TEAEs)", which the company defined as "starting on or after the day of first dose of study medication, and included up to 30 days after double-blind study drug discontinuation or the day before the start of open-label siponimod, whichever came first." The ERG note that AE were assessed at each study visit (CSR, page 38). Detailed tables of safety data are provided in the CS: Table 43-49 pages 79-86. The ERG have provided a summary of AE as reported in the EXPAND trial publication in Table 13

Table 13.[2]

The EXPAND trial publication reports the following "*1645 patients were included in the safety set: 1099 on siponimod and 546 on placebo*".[2] The CS states that TEAEs were observed in the majority of patients and were observed in a higher proportion of patients randomised to siponimod (88.7%) compared to placebo (81.5%) (CS Document B Table 43, page 80).

A total of 197 (18%) patients on siponimod and 83 (15%) on placebo had at least one serious AE.[2]

The most frequently reported TEAEs (in at least 10% of patients per group) were: headache, nasopharyngitis, urinary tract infection, and fall. There were no differences in the rate of infection AEs between the treatment groups, however there was an increase in the rate of serious infections, for the siponimod group compared with the placebo group ([redacted] and [redacted], respectively). Four deaths occurred in each treatment group.[2] The ERG examined the reported cause of death in the EXPAND trial, and noted that deaths in the siponimod group were due to melanoma, septic shock, urosepsis and suicide.

A total of [redacted] of patients in the siponimod group and [redacted] in the placebo group had TEAEs leading to study drug discontinuation (most common: macular oedema, alanine aminotransferase increased, and bradycardia). During clarification (A9b), the ERG requested data regarding the number of patients switching to open label treatment and/or how many patients stopped treatment altogether. The company provided Table 12 in response to this clarification question. However, the ERG note the data presented is only for patients who reach 6-month CDP.

Table 12. Premature discontinuation of double-blind study drug after reaching 6-month CDP

Prematurely discontinued double-blind study drug during Treatment Epoch[a]	**Siponimod N=1,105 n (%)**	**Placebo N=546 n (%)**	**Total N=1,651 n (%)**
Switched to open-label siponimod treatment	[redacted]	[redacted]	[redacted]
Stopped treatment and switched to abbreviated visit schedule (i.e. stopped treatment)	[redacted]	[redacted]	[redacted]
Discontinued Treatment Epoch directly from study drug	[redacted]	[redacted]	[redacted]
Footnotes: [a] Patients who discontinued prematurely from the study drug are defined as patients who have been exposed to the study drug and did not complete the Treatment Epoch on the study drug.			

The ERG note that siponimod was generally well tolerated. A higher percentage of siponimod (81.7%) compared to placebo (77.7%) patients completed the treatment period.

The EXPAND publication suggests that the safety profile of siponimod is generally aligned with that of other drugs in the class.[2] The ERG notes that long-term safety outcomes are not yet available. The company note two ongoing studies

- Open-label extension part of the EXPAND trial; NCT01665144.[37]

- Phase III study: Safety and tolerability of conversion from oral or injectable DMTs to dose-titrated oral siponimod in advancing patients with RMS (EXCHANGE); NCT03623243.[38]

Table 13 Safety outcomes (adverse events) as reported in EXPAND trial publication.2

Adverse event	Siponimod	Placebo	Difference between the study groups
At least one adverse event	975 (89%)	445 (82%)	Not reported
At least one serious adverse event	197 (18%)	83 (15%)	
Discontinued because of an adverse event, including serious and non-serious AEs	84 (8%), of which 36 were serious and 48 non-serious	28 (5%), of which 13 were serious and 15 non-serious	
Death	4 (<1%)	4 (1%)	
Areas of interest with S1P-receptor modulators			
Liver-related investigations, signs and symptoms (SMQ broad)	135 (12%)	21 (4%)	Not reported
Hypertension (SMQ narrow)	137 (12%)	50 (9%)	
Hypertension (PT)	115 (10%)	41 (8%)	
Thromboembolic events (NMQ)	33 (3%)	15 (3%)	
Infections and infestations (SOC)	539 (49%)	268 (49%)	
Herpes viral infections (HLT)	53 (5%)	15 (3%)	
Herpes zoster (PT)	25 (2%)	4 (1%)	
Skin neoplasms, malignant and unspecified (SMQ narrow)	14 (1%)	8 (1%)	
Lymphopenia (PT)	9 (1%)	0	
Lymphocyte count decreased (PT)	4 (<1%)	0	
Oedema peripheral (PT)	50 (5%)	13 (2%)	
Macular oedema (PT)	18 (2%)	1 (<1%)	
Convulsions (including all types of seizure; SMQ broad)	19 (2%)	2 (<1%)	
Bradycardia (PT) during treatment initiation	48 (4%)	14 (3%)	
Bradyarrhythmia (including conduction defects and disorders of sinus node function; SMQ broad) during treatment initiation	29 (3%)	2 (0·4%)	
Sinus bradycardia (PT) during treatment initiation	14 (1%)	1 (<1%)	
Serious adverse events occurring in ≥0·5% of patients in either group			
Alanine aminotransferase increased	10 (1%)	2 (<1%)	Not reported
Aspartate aminotransferase increased	5 (<1%)	1 (<1%)	
Basal cell carcinoma	11 (1%)	6 (1%)	
Concussion	5 (<1%)	0	
Depression	5 (<1%)	2 (<1%)	
Urinary tract infection	13 (1%)	6 (1%)	
Suicide attempt	4 (<1%)	3 (1%)	

Gait disturbance	1 (<1%)	3 (1%)	
Multiple sclerosis relapse	2 (<1%)	7 (1%)	
Paraparesis	0	3 (1%)	
HLT=high-level term; NMQ=Novartis MedDRA query; PT=preferred term; SMQ=standardised MedDRA query; SOC=system organ class			

4.2.8 Summary of the critique of EXPAND, analysis and interpretation

The EXPAND[2] study was a double-blind phase-III placebo-controlled randomised trial which assessed the effectiveness and safety of siponimod. This was the only study included in the CS that provided clinical effectiveness data for siponimod in patients with SPMS.

In EXPAND,[2] siponimod displayed a significant improvement compared with placebo for the following outcomes:

- 3-month CDP (HR)=0.79; 95% CI: 0.65, 0.95)
- 6-month CDP (HR=0.74; 95% CI: 0.60, 0.92)
- annualised relapse rate (ARR) (HR= 0.45; 95% CI: 0.34, 0.59)
- time to confirmed first relapse (HR= 0.54; 95% CI: 0.41, 0.70)
- various cognitive measures and MRI-related outcomes (T2 lesion volume, brain volume, presence of gadolinium-enhancing lesions, new or newly enlarging T2 lesions).

Siponimod was not significantly different from placebo for the following outcomes:

- time to 3-month ≥20% worsening in T25FW from baseline (HR= 0·94; 95% CI: 0.80, 1.10)
- between-group difference in the mean MSWS-12 score change from baseline at 12 (-1.83; 95% CI: -3.85, 0.19)
- between-group difference in the mean MSWS-24 score change from baseline at 24 months of follow-up (-1.23; 95% CI: -3.89, 1.44).

The occurrence of at least one serious AE in the siponimod group was slightly higher than in the placebo group (18% vs. 15%). However, all of which have been described previously in the context of S1P-receptor modulation in MS.[2]

4.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

The following section provides a critique of the indirect comparison conducted by the company. The MAIC entailed the comparison of aggregate data from six studies for the three key outcomes: 3-month CDP, 6-month CDP and ARR.

4.3.1 Trials identified and included in MAIC

The company conducted a SLR of studies reporting comparative effectiveness and safety of siponimod and other treatments in patients with SPMS. All trials of comparator treatments (i.e., DMTs) licensed for MS or used in clinical practice for treatment of SPMS across the UK were eligible for inclusion.

Critique of searches, study inclusion/selection, and data extraction performed for the CS SLR is provided in Section 4.1. The SLR identified 23 unique studies, of which only six were deemed eligible for inclusion in the analysis of indirect treatment comparison (CS Appendix D, page 83). The six studies were randomised double-blind placebo-controlled trials of efficacy and safety of siponimod (EXPAND),[2] natalizumab (ASCEND),[4] interferon beta-1b (EU study, NA study),[7-9] and interferon beta-1a (SPECTRIMS, IMPACT),[5, 6, 10] in patients with SPMS (Table 14).

The primary end-point for the comparator trials was CDP, but with different definitions and study durations. However, as all of the studies used the EDSS, it was possible to compare the results with those from the EXPAND study.[2] Further details on baseline patient characteristics of the included comparator treatment studies are presented in Section 4.3.1.1 as well as ERG Appendix A.

Table 14. Studies included for indirect treatment comparison

Study Name Year	Interventions/sample size (n)	Relapse-free in 2 years prior to study n (%)	Study duration
EXPAND 2018[2]	Siponimod (2 mg PO QD); n=1105 Placebo; n=546	712 (64) 343 (63)	3 years
ASCEND 2018[4]	Natalizumab (300 mg IV Q4W); n=439 Placebo; n=448	312 (71) 315 (70)	2 years
SPECTRIMS 2001 [5, 6]	Interferon beta-1a (22 µg SC TIW); n=209 Interferon beta-1a (44 µg SC TIW); n=204 Placebo; n=205	113 (54) 106 (52) 107 (52)	3 years
NA study 2004[7]	Interferon beta-1b (160 µg SC Q2D); n=314 Interferon beta-1b (250 µg SC Q2D); n=317 Placebo; n=308	173 (55) 170 (54) 174 (56)	3 years*
EU study 1998, 2001[8, 9]	Interferon beta-1b (250 µg SC Q2D); n=360 Placebo; n=358	115 (31.9) 101 (28.2)	3 years**
IMPACT 2002[10]	Interferon beta-1a (60 µg IM QW); n=217 Placebo; n=219	NR	2 years

NA=North American; EU=European; IV=intravenous; PO=oral; QD=once daily; SC=subcutaneous; TIW=three times a week; Q2D=once every two days; Q4W=once every 4 weeks; IM=intramuscular; QW=once weekly; NR=not reported
*Early termination for the 250 µg group (mean follow-up: 998 days) and 160 µg group (mean follow-up: 1013 days)
**Early termination for the 250 µg group at month 33 (mean follow-up: 1068 days)

The reasons for exclusion of the remaining 17 trials were (provided during clarification A14) as follows:

- Ineligible treatments not licensed for MS in the UK (n=11 trials; biotin, simvastatin, rituximab, mitoxantrone, cyclophosphamide, fluoxetine, masitinib, stem cell therapy, and idebenone)[39-49]
- Used only as induction therapy (n=2 trials; cladribine)[50, 51]
- Not reporting CDP and ARR outcomes (n=3 trials)[52-54]
- Unlicensed dose regimen (n=1 trial)[55]
- Different outcome definition (1 trial)[51]

The ERG note that the IMPACT study,[10] (which compared interferon β-1a (60 µg QW) to placebo) did not use the authorised dose (30 µg) of the drug, however, the company still retained the study in the evidence synthesis and MAIC analysis. The company justified the inclusion by stating that no additional benefit had been shown by administering a higher dose once a week, and therefore it could be assumed that the efficacy of the 60 µg dose is the same as for the licensed 30 µg dose. The ERG consider that this decision contradicts the company decision problem which limited DMTs within their MA for RRMS (see Section 3.3).

4.3.1.1 Assessment of feasibility of indirect comparisons

In the absence of RCT reporting comparative efficacy and safety between siponimod and DMTs licensed for MS or used in clinical practice for treatment of SPMS, it is of interest to compare these treatments using aggregate data-based standard methods for indirect comparisons (e.g., NMA), proposed by Bucher et al.[56] Conventionally, NMA is conducted in the presence of studies with common comparator arms (e.g., placebo) and its validity is based on the key assumptions of transitivity (i.e., constancy of relative effects; similarity in cross-trial distribution of Effect Modifiers [EM]) and consistency (i.e., coherence; agreement between direct and indirect treatment effect estimates).[57]

Following the NICE Decision Support Unit (DSU) Technical Support Document (TSD),[57] the company examined the feasibility of NMA across the publications of the EXPAND trial[2] and the five RCTs (listed in Table 14) of comparator treatments used in patients with SPMS. They aimed to determine if EM are present and if there is an imbalance between the trial populations.

4.3.1.2 Pair wise comparisons between EXPAND and the included trials

The company compared the following items in a pairwise fashion between EXPAND[2] and the remaining five trials (CS Document B, Table 32-36):

- study design
- study inclusion/exclusion criteria
- baseline patient characteristics (i.e., treatment EM)
- outcome definitions
- placebo-arm outcomes.

The company assessed the degree of difference between trials by comparing the trial features either qualitatively or quantitatively (CS Appendix D, page 87-115). Limited information was provided in the CS to demonstrate how the qualitative assessments were conducted (e.g., individual or double assessment, how conflicts were resolved). Each characteristic was assessed using a threshold of +/-10% difference (see CS Appendix D Tables 19- Table 48) (e.g., ✓ = Studies are similar, differences within the threshold of 10%; ! = Differences exist between the trials which exceeded 10% still considered feasibly comparable, X= differences exceeding 10%, and were impossible to accommodate through matching or adjusting).

The company provided the following statement regarding the selection of +/-10% threshold *"this was a subjective judgement and a difference of greater than 10% does not necessarily indicate that the characteristic in question is a driver for bias. A characteristic greater than the 10% threshold was flagged as dissimilar and considered as a potential source of heterogeneity and/or bias, which could present a weakness of indirect comparisons."* Although the ERG agrees that differences between studies should be considered as a potential source of heterogeneity, we highlight the arbitrary selection of the +/-10% threshold. This could identify differences between studies which may not be clinically meaningful.

4.3.1.3 Comparisons across all included trials

The comparisons of inclusion/exclusion criteria, outcome definitions, and baseline patient characteristics across all six trials were also compared either qualitatively or quantitatively (Table 15 to Table 17). The ERG consider that the comparator trials generally had similar inclusion/exclusion criteria.

Quantitative comparisons were performed for: (*Table 17*)

- Baseline patient characteristics –age, gender, mean EDSS score, duration of SPMS, history of IFN/DMT therapy, normalised brain volume, proportion of patients with Gd + lesions on T1-weighted image, total volume of T2 lesions, number of relapses in prior year/2 years, mean timed 25-foot walk test, proportion of patients relapse-free in prior year/2 years (standardized mean difference/SMD: minimal [SMD<0.1], moderate [0.1≤SMD<0.2], and major [SMD≥0.2])

The ERG note that the quantitative assessment of baseline patient characteristics were based on assessment of standardised mean difference (SMD) between trials for each factor (see footnote *Table 17*). Categorisation using this method resulted in various characteristics rated as having 'major' differences (for example, comparison between EXPAND and NA study the mean [SD] EDSS score, mean [SD] duration of MS in years, proportion of patients without previous use of a DMT*). The ERG examined the citation provided to justify the SMD ≥0.2 threshold.[58] We note that the publication provides some rationale for the 0.2 SMD threshold, although we could not identify why a 0.2 difference is expected.

Qualitative comparison were performed for:

- Study design (design, MS population, placebo administration, study duration)

- Study inclusion/exclusion criteria (MS population, EDSS range, age range, prior IFN therapy, # of relapses in X time prior to trial entry, progression of disability documented within X time prior to trial entry, history of RRMS, duration of MS, duration of SPMS, MS severity score, T25FW test)

- Outcome definitions (annualised relapse rate/ARR, time to 3-month CDP, time to 6-month CDP, and discontinuation)

- Placebo-arm outcome (difference in annualised relapse and discontinuation rates: > 10% [deemed as different] vs. ≤10% [deemed as similar])

Table 15. Inclusion/exclusion criteria in the trials in MAIC: pairwise comparison (EXPAND vs. another trial)

Inclusion/exclusion criteria	EXPAND [2]	ASCEND [4]	NA STUDY [7]	IMPACT [10]	SPECTRIMS [5, 6]	EU STUDY [8, 9]
MS population	SPMS	SPMS (V)	SPMS(V)	SPMS(V)	SPMS(V)	SPMS(V)
Baseline EDSS range	3.0-6.5	3.0-6.5 (V)	3.0-6.5 (V)	3.5-6.5 (!)	3.0-6.5 (V)	3.0-6.5 (V)
Age range (years)	18-60	18-58 (!)	18-65 (XX)	18-60 (V)	18-55 (!)	18-55 (!)
Prior IFNβ therapy	Yes	No IFNβ use 4 weeks prior to study (V)	No prior interferon β use (!)	No prior interferon β use (!)	No prior interferon β use (!)	No prior interferon β use (!)
Number of relapses in X months prior	3 months	3 months (V)	2 months (XX)	NR (NA)	2 months (XX)	1 month (XX)
Documented progression within X months prior	24 months	12 months (!)	24 months and ≥ 1 relapse with progressive deterioration for ≥6 months (XX)	12 months (!)	6 months (!)	24 months (V)
History of RRMS	Required	NR (NA)	Required (V)	NR (NA)	Required (V)	Required (V)
Duration of MS	Any	NR (NA)	≥ 2 years (!)	NR (NA)	NR (NA)	≥2 years
Duration of SPMS	Any	≥ 2 years (!)	NR (NA)	NR (NA)	NR (NA)	NR (NA)
MS severity score	Any	≥4 (!)	NR(NA)	NR(NA)	NR(NA)	NR(NA)
T25FW test score	Any	<30 sec (!)	NR(NA)	NR(NA)	NR(NA)	NR(NA)
Active SPMS definition	Relapses in 2 years prior study or Gd+ T1 lesions at baseline	NR (NA)	NR (NA)	Relapses in year before enrolment (!)	Relapses in 2 years before the study (!)	Relapse within 2 years before the study (!)

NA=North American; EU=European; NR=not reported; SPMS=secondary progressive multiple sclerosis; IFNβ=interferon beta; T25FW=Timed 25-Foot Walk; RRMS=relapse-remitting multiple sclerosis; sec=seconds; EDSS= expanded disability status scale; V=criterion is identical or similar (EXPAND vs. another trial); !=different but EXPAND population broader vs. another trial (matching maybe possible); XX= different and EXPAND population not broader vs. another trial (matching not possible); NA=not applicable as not reported

Table 16. Comparison of outcome definitions in the trials in MAIC: pairwise comparison (EXPAND vs. another study)

Study	Annualised relapse rate (ARR)	Time to 3-month CDP	Time to 6-month CDP	Discontinuation
EXPAND[2]	# total relapses per PYs	1.0-point ↑ in EDSS score: 3.0-5.0 0.5-point ↑in EDSS score: 5.5-6.5	1.0-point ↑ in EDSS score: 3.0-5.0 0.5-point ↑in EDSS score: 5.5-6.5	The proportion of randomised patients who discontinued treatment for any reason
ASCEND[4]	# total relapses per PYs (V)	NR (NA)	1.0-point ↑ in EDSS score: 3.0-5.5 0.5-point↑ in EDSS score: 6.0-6.5 and ≥20% in T25FW Inc. ≥20% in 9-HPT (XX)	The proportion of randomised patients who discontinued treatment for any reason (V)
NA STUDY[7]	# total relapses per PYs (V)	NR (NA)	1.0-point ↑ in EDSS score: 3.0-5.5 0.5-point ↑in EDSS score: 6.0-6.5 (!)	The proportion of randomised patients who discontinued treatment for any reason (V)
IMPACT[10]	# total relapses per PYs (V)	11.0-point ↑ in EDSS score: 3.0-5.5 0.5-point ↑in EDSS score: 6.0-6.5 (!)	NR (NA)	The proportion of randomised patients who discontinued treatment for any reason (V)
SPECTRIMS[5, 6]	# total relapses per PYs (V)	1.0-point ↑ in EDSS score: 3.0-5.0 0.5-point ↑in EDSS score: 5.5-6.5 (V)	NR (NA)	The proportion of randomised patients who discontinued treatment for any reason (V)
EU STUDY[8, 9]	# total relapses per PYs (V)	1.0-point ↑ in EDSS score:3.0-5.5 0.5-point ↑in EDSS score: 6.0-6.5 (!)	NR (NA)	The proportion of randomised patients who discontinued treatment for any reason (V)

PYs=patient-years; #=number; ↑=increase; NA=North American; EU=European; NR=not reported; EDSS= expanded disability status scale; V=criterion is identical or similar (EXPAND vs. another trial); !=different but EXPAND population broader vs. another trial (matching maybe possible); XX= different and EXPAND population not broader vs. another trial (matching not possible); NA=not applicable as not reported; T25FW=Timed 25-Foot Walk; 9-HPT= Nine Hole Peg Test

*Table 17. Baseline patient characteristics in the trials in MAIC and pairwise comparison based on standardised mean difference: Siponimod group (of the EXPAND study) vs. Comparator treatment group (of the comparator treatment study)**

Baseline patient characteristics	EXPAND [2]	ASCEND [4]	NA STUDY [7]	IMPACT [10]	SPECTRIMS [5, 6]	EU STUDY [8, 9]
Mean (SD) Age in years	48 (7.8)	47.2 (7.6) (mod)	46.8 (8.1) (mod)	47.6 (7.9) (min)	42.8 (7.1) (maj)	41 (7.2) (maj)
Proportion female (%)	60	62 (min)	63 (min)	64 (min)	63 (min)	61(min)
Mean (SD) EDSS score	5.4 (1.1)	5.6 (0.9) (mod)	5.1 (1.2) (maj)	5.2 (1.1) (min)	5.4 (1.1) (min)	5.1 (1.1) (maj)
Proportion of patients with EDSS score ≥6.0 (%)	[redacted]	63 (mod)	NA	48 (mod)	NA	45 (maj)
Mean (SD) time since onset of MS symptoms in years	17.1 (8.4)	16.8 (7.6) (min)	NA	NA	NA	NA
Mean (SD) duration of MS in years	12.9 (7.9)	12.1 (6.9) (min)	14.7 (8.3) (maj)	16.5 (9.0) (maj)	13.3 (7.7) (min)	13.1 (7.0) (min)
Mean (SD) duration of SPMS in years	3.9 (3.6)	4.8 (3.4) (maj)	4.0 (3.4) (min)	NA	4.0 (3.0) (min)	2.2 (2.3) (maj)
Mean (SD) normalised brain volume (cm^3)	1,423 (86.0)	1,421 (82·8) (min)	NA	NA	NA	NA
Proportion of patients with Gd+ lesions of T1-weighted images (%)	21	24 (min)	NA	36	NA	NA
Mean (SD) total volume of T2 lesions on T2-weighted images (mm^3)	15,321 (16,268)	16,793 (17,003) (min)	NA	NA	NA	NA
Proportion of patients without previous use of a DMT (%)	22	23 (min)	100* (maj)	100*(maj)	100*(maj)	100 (maj)
Time since most recent relapse (months)	[redacted]	57 (49.2) (min)	NA	44.4 (60.0) (maj)	NA	NA
Proportion of patients relapse-free in prior year (%)	[redacted]	84 (mod)	NA	61 (maj)	NA	NA
Proportion of patients relapse-free in prior 2 years (%)	[redacted]	71 (mod)	55 (mod)	NA	53 (maj)	32 (maj)
Mean (SD) number of relapses per patient in the prior year	0.2 (0.5)	NA	NA	0.6 (1.1) (maj)	NA	NA
Mean (SD) number of relapses per patient in the previous 2 years	0.7 (1.2)	NA	0.8 (1.3) (mod)	NA	0.9 (1.3) (mod)	NA

DMT=disease-modifying therapy; SPMS=secondary progressive multiple sclerosis; NA=North American; EU=European; NR=not reported; T25FW=Timed 25-Foot Walk; EDSS= expanded disability status scale; NA=not applicable as not reported; SMD= standardised mean difference; min= minimal degree of difference (SMD <0.1); mod = moderate degree of difference (SMD ≥0.1 and <0.2); maj = major degree of difference (SMD ≥0.2)

*SMD thresholds based on Austin 2009[58]**A value of 100% was assumed because IFN-experienced patients were excluded at screening, as described in the exclusion criteria of the trial, and other DMTs were not available at the time of enrolment

4.3.1.4 Effect modifiers

The EM were identified separately for CDP (10 EM) and ARR (5 EM) outcomes through the combination of *a priori* evidence (derived from a univariate regression analysis of EXPAND IPD) and clinical opinion from experts attending two Novartis-organised advisory boards (one in the UK, one in Canada) (CS Document B, page 66). Details regarding the process to select experts, or their conflicts of interest was not provided in the CS.

The ERG consider that the process used to identify EM lacked transparency. According to NICE TSD18,[57] MAIC requires there to be strong evidence of effect modification occurring to justify using anchored MAICs. The ERG consider that the company has not presented strong evidence to suggest important treatment effect modification is occurring. The company identified age, EDSS, MS duration, SPMS duration, number of relapses in prior 2 years and sex as potential effect modifiers based the opinion of clinicians who took part in the consensus advisory boards organised by the company.

The ERG conducted a visual inspection of the summary forest plot from the EXPAND[2] study included in the CS appendix D.1.5 (page 85-86) and suggest that there is considerable overlap in the hazard ratios across categories: for example age: <42 HR 95% CI, 0.58 (0.38, 0.90), > = 42 HR 95% CI, 0.79 (0.62, 1.01). Given that the HR are generated from the EXPAND study[2] which has relatively large sample size (1683), we would expect there to be little overlap in hazard ratios across age categories for age to be important moderator of treatment effect. Similar conclusions can be drawn across levels of the other variables the company considered to be important EM.

The ERG conducted further exploration of the EM using the univariate analysis of 6-month CDP and 3-month CPD outcomes provided by the company in CS Appendix D (Figure 3 and Figure 4). Univariate analysis of ARR was not provided in the CS. The ERG have presented Figure 3 below as 6-month CDP is a key input into the economic base-case (see ERG appendix C for 3-month CPD and proportion with 6-months [96w] CDP outcomes).

The ERG note that there is considerable overlap in hazard ratios across levels of the stratification variables. Given the wide CIs the interpretation is limited regarding the presence of any effect modification. The ERG clinical advisor stated that "*none of the event modifiers looks to have a dramatic effect*". And questioned "*why they [the company] presented relapses in prior year or 2 years as*

yes/no…and then for yes as 1 or more than one [which] should be single analysis for each with 0, 1 or >1." The ERG were unable to find a justification for the cut-offs the company impose on the continuous variables. It appears that some variables are split by medians (e.g., volume of T2 lesions), however others are not e.g., age.

The ERG clinical advisor confirmed that "*there is not much difference in the effect between the two coupled variables*". The only exception is MS duration where the treatment effect seems to differ in substantial way between the duration <11.9 versus duration greater than 11.9 (Table 18). The ERG note that this is the only variable suggestive of possible effect modification, we found no evidence in the CS as to why 'MS duration since diagnosis (years)' was split into <11.9 and >=11.9. Therefore, we asked our clinical expert who stated that there was no clinical rationale to split the variable at 11.9, suggesting instead that "*if it is an arbitrary cut off, then 12 makes more sense than 11.9*."

Figure 3. Univariate regression analysis for time to 6-month CDP from the EXPAND trial

Table 18. Univariate analysis of the effect modifiers

Effect modifiers	Subgroup	Siponimod, N (%)	Placebo, N (%)	HR (95% CI)
Overall	[redacted]	[redacted]	[redacted]	[redacted]
Age	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
EDSS score at screening	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
MS duration since diagnosis	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
Duration of SPMS	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
Number of relapses in prior 2 years	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
Sex	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]

The overlap between groups and wide CIs for each EM limits the interpretation of the variables the company present as EM (see Table 18). We also note that the sample size is sufficiently large in the EXPAND trial.[2] The ERG's preference would be to re-run this analysis on continuous variables, without grouping them as the company has done. However, this was not possible without the IPD from the EXPAND trial.

4.3.1.5 ERG feasibility of indirect comparisons

The company concluded that although all six trials had a common comparator/anchor (i.e., placebo), there were marked cross-trial differences in the following; study design (study duration, placebo administration), populations (study inclusion/exclusion criteria, baseline patient characteristics), placebo-arm outcomes (annualised relapse and discontinuation rates), outcome definitions (for time to CDP) (CS Document B, pages 67-73; Tables 32-38 and CS-Appendix D, page 87-11). The ERG agree that there were differences across the six trials in study design, populations, placebo-arm outcomes and outcome definitions as outlined in Table 15 to Table 17.

Based on the NICE DSU TSD,[57] guidance the company determined that an anchored MAIC would be the most appropriate and robust analytical method to compare siponimod to other SPMS treatments. The company justified the use of the anchored MAIC by stating that the use of IPD from EXPAND[2] trial in MAIC would allow the company to match and adjust some of the (if not all) observed cross-trial

imbalances in trial features (patient inclusion/exclusion criteria, outcome definition) and EM between the EXPAND^2 trial and other trials for which only aggregate data were available and provide more valid and robust indirect comparison estimates than standard NMA (CS-Document B, page 63; CS-Appendix D, page 87-115).

The company stated that failure to account for differences observed across the six trials could undermine the validity of NMA, resulting in biased treatment effect estimates. The ERG deem this statement to be correct, however the same statement can be made for the CS MAIC. The company concluded that the conduct of NMA was not feasible, since transitivity and consistency would be violated, stating that "*the presence of significant clinical heterogeneity, inconsistency and dissimilarity, as well as an imbalance of effect modifiers between EXPAND and each of the comparator trials undermines the validity of ITC methods that are based on summary-level data, such as an NMA"* (CS Document B, page 72). The ERG note that if EM are clearly different between the trials, then an NMA should not be attempted, however as described in Section 4.5 we do not consider the assessment of transitivity to be fully explored in the CS.

The ERG considered that the results of the six included studies (intervention vs. comparator) and the feasibility of NMA should be explored further due to:

- lack of EXPAND IPD to independently appraise the CS EM and MAIC
- lack of transparency of the selection of EM (clinical opinion)
- considerable overlap of stratification variables (Figure 3)
- matching and adjustment was not be possible for all factors considered in the MAIC.

The ERG conducted an exploratory NMA for all outcomes using aggregate data from EXPAND^2 and where possible, the five included comparator studies (SPECTRIMS, NA Study, EU Study, ASCEND, and IMPACT) (see Section 4.5 and ERG appendix C). The ERG note that the effect estimates from the ITC for 6-months CDP and ARR outcomes are key inputs for the economic model base-case (see Section 6.2) The ERG evaluate transitivity for 6-month CDP in Section 4.5 to assess the similarity in cross-trial distribution of EM. The ERG highlight that inconsistency could not be assessed (graphically or statistically) as the comparison networks did not contain closed loops (exploratory NMA for 3-month CDP and proportion with 6-months (96w) CDP outcomes are provided in ERG appendix C).

4.3.2 Methods used in MAIC

The company conducted a placebo-anchored MAIC to compare the efficacy of siponimod to other DMTs for the treatment of adults diagnosed with SPMS (CS Appendix D, page 83). The analysis of MAIC was based on the ITT populations of the included studies. A MAIC analysis for the active SPMS subgroup was not feasible (see Sections 4.2.6.1 and **Error! Reference source not found.**). There was a lack of reporting of definitions of active SPMS in the NA study[7] and the ASCEND study.[4] Moreover, the SPECTRIMS study, [5, 6] the EU study,[8, 9] and the IMPACT study[10] did not report baseline characteristics and relevant outcomes for this subgroup separately (CS-Document B, page 72; Tables 39-40).

4.3.2.1 Risk of Bias assessment

The company assessed the RoB of six included trials conducted in patients with SPMS using a RoB tool (CS Document B, page 38) adapted from the tool developed at the CRD, University of York (domains assessed included: randomisation, allocation concealment, blinding [participants, study personnel, and outcome assessors], similarity of groups at baseline, selective outcome reporting, and sample attrition/incomplete/missing outcome data). RoB assessments are provided in CS Document B (page 38) and CS Appendix D (pages 141-143, Tables 60-61).

The ERG were not certain as to whether or not the CS assessments were done by a single or two (or more) independent reviewers. The company only included justifications supporting the assessment for the EXPAND study[2] (see Section 4.1.4 and Appendix D, page 143, Table 61). Two ERG reviewers (J.P. and A.T.) independently assessed the RoB of all included trials using the same tool as was used in the CS. Any disagreements were resolved by a discussion or help of a third adjudicator (A.G.). The RoB assessed by the company and ERG are provided in ERG Appendix B.

In general, most RoB domains of all six RCTs were rated as low RoB by the company and the ERG, showing a good agreement. There were a few disagreements. For example, the company assigned low RoB and the ERG assigned unclear RoB rating to randomisation (EU study, IMPACT)[8-10] allocation concealment (NA study, IMPACT),[7, 10] and high RoB to imbalance in baseline characteristics (SPECTRIMS).[5, 6] Conversely, the ERG judged blinding to be at low RoB in two studies (EU study, IMPACT),[8-10] whereas the company rated the same domain in these studies as unclear RoB.

4.3.2.2 Network of evidence

The EXPAND^2 trial and all of the comparator trials were connected by their comparisons to placebo (anchored MAIC), which is a standard ITC with a common comparator for the treatment in the network. As comparisons were anchored, adjustment was only required for treatment EM, see Section 4.5.

The matching step was performed to align patient inclusion/exclusion criteria in the EXPAND^2 study to those of the other comparator DMT trials. If the inclusion criteria in EXPAND^2 study were broader (for example, males and females) compared to the comparator trial (e.g., females only), patients who would not meet the criteria in the latter (i.e., males) were excluded from the EXPAND^2 study IPD set. However, the matching was infeasible if the inclusion criteria in EXPAND^2 study were narrower (e.g., females only) compared to those in the comparator trial (males and females), since it would not be possible to exclude males from the comparator trial given the lack of access to IPD of the comparator trial. Only those inclusion/exclusion criteria that were reported in a publication of the comparator trial were used for matching.

The ERG note that the company did not provide the EXPAND^2 study IPD set in the CS or following the ERG clarification request (A18, B2). Without access to the IPD from the comparator trials in the MAIC, the ERG is concerned that there may still be residual unobserved differences and potential sources of bias even after matching has occurred.[59]

In the adjustment step, patients in the EXPAND^2 trial IPD were re-weighted to make the distribution of important EM (baseline patient characteristics) in the sample source similar to those in the competitor trials (e.g., ASCEND). The weights (i.e., propensity scores) were estimated as the odds of being in the EXPAND study versus the competitor trial (e.g., ASCEND study) in a regression model adjusted for all EM using the generalised method of moments based on IPD and aggregate data. The EM were identified and ranked for importance separately for CDP (10 EM) and ARR (5 EM) to assess relationships between covariates and outcomes (see Table 19).

Table 19. Treatment effect modifiers (baseline patient characteristics) used for adjustment

Rank	Adjustment factor (treatment effect modifier)
Confirmed disability progression (CDP)	
1	Age
2	EDSS score at screening
3	Duration of MS since diagnosis
4	Treatment experience (IFN or DMT history)
5	Normalised brain volume
6	Gadolinium-enhancing lesions on T1-weighted images
7	Duration of SPMS
8	Total volume of T2 lesions on T2-weighted images
9	Number of relapses in prior 2 years (or any other relapse variable)
10	Sex
Annualised relapse rate (ARR)	
1	Time since onset of most recent relapse
2	Number of relapses per patient in one year prior to study
3	Number of relapses per patient in two years prior to study
4	Gadolinium-enhancing lesions on T1-weighted images
5	Total volume of lesions on T2-weighted images

SPMS=secondary progressive multiple sclerosis; EDSS= expanded disability status scale; IFN=interferon; DMT=disease-modifying therapy; CDP=confirmed disability progression; ARR=annualised relapse rate

Given that indirect comparisons were anchored, the propensity weighting regression models were adjusted for all identified and reported EM, but not for purely prognostic factors in order to avoid inflated standard errors due to overmatching effects. The ERG note that according to the NICE DSU TSD guidance, the between-trial differences in the distribution of prognostic factors (which are not necessarily EM) do not affect the relative treatment effects as a result of their balanced distribution between the treatment groups due to randomisation (assuming a sufficiently large sample size).

The company provided the unmatched, matched unadjusted, as well as matched and adjusted results of MAIC (e.g., ESS, mean and standard deviations of EM used in the adjustment model, and outcome effect estimates for CDP and ARR), see Section 4.5 for ERG critique of the three populations used in the MAIC. The matched and adjusted results were provided by considering multiple scenarios starting from scenario A (adjusted for all ranked EM – the most conservative result) with following scenarios (e.g., B, C, D etc…) in each of which the lowest ranked EM was dropped out of the regression model. The ERG note that Scenario A was used in the company's base case analysis, see Section 6.2.

4.3.3 Results of MAIC

This section presents the results of the matching and adjustment process, and the overall results of the MAIC analysis.

4.3.3.1 Matching results

The company was able to match some, but not all inclusion/exclusion criteria between the EXPAND IPD and the five comparator treatment trials (CS Appendix D; pages 115-136). Table 20 and Table 21 provide the inclusion and exclusion criteria for the EXPAND study[2] and a concise summary of the matching process between the EXPAND study and the five comparator treatment trials. More details describing the actions applied to achieve matching for each pair of trials (EXPAND study vs. comparator treatment trial) are provided in CS Appendix D (pages 115-136).

Table 20. The inclusion and exclusion criteria for the EXPAND2 trial

Inclusion/exclusion criteria	EXPAND study[2]
MS population	SPMS
Baseline EDSS Range	3.0-6.5
Age Range (years)	18-60
Prior IFN Therapy	Allowed
No Recent Relapse in Specified Time-Frame	<3 months
Documented Progression in Specified Time-Frame	24 months (progression of at least 6 months)
Duration of MS	No restriction
Duration of SPMS	No restriction
MS Severity Score	No restriction
T25FW Test Score	No restriction
Active SPMS definition	Presence of relapses in 2 years before study or Gd+ T1 lesions at baseline

EDSS=expanded disability status scale; IFN= interferon; MS= multiple sclerosis; SPMS=secondary progressive multiple sclerosis; T25FW= timed 25-foot walk test; NR=not reported

Table 21. Results for matching on inclusion/exclusion criteria for EXPAND2 trial vs. comparator treatment trials

Inclusion/exclusion criteria	SPECTRIMS [5, 6]	NA STUDY [7]	EU STUDY [8, 9]	ASCEND [4]	IMPACT [10]
Adults with SPMS	Matched	Matched	Matched	Matched	Matched
	Identical criteria	Identical criteria	Identical criteria	Identical criteria	Identical criteria
Baseline EDSS Range	Matched (3.0-6.5)	Matched (3.0–6.5)	Matched (3.0–6.5)	Matched (3.0–6.5)	Matched (3.0–6.5)
	Removed patients with baseline EDSS score <3.0 and >6.5 (in EXPAND)	Removed patients with baseline EDSS score <3.0 and >6.5 (in EXPAND)	Removed patients with baseline EDSS score <3.0 and >6.5 (in EXPAND)	Removed patients with baseline EDSS score <3.0 and >6.5 (in EXPAND)	Removed patients with baseline EDSS score <3.0 and >6.5 (in EXPAND)
Age Range (years)	Matched (18–55)	Not matched (18–65)	Matched (18–55)	Matched (18–58)	Matched (18–60)
	Removed patients >55 years (in EXPAND)	Narrower criteria 18-60 years (in EXPAND)	Removed patients >55 years (in EXPAND)	Removed patients >58 years (in EXPAND)	Identical criteria (in EXPAND)
Prior IFN Therapy	Matched (Prior interferon therapy ineligible)	Matched (Prior interferon therapy ineligible)	Matched (Prior interferon therapy ineligible)	Not matched (Excluded if within 4 weeks prior to randomization)	Matched (Prior interferon therapy ineligible)
	Interferon users excluded (in EXPAND)	Interferon users excluded (in EXPAND)	Interferon users excluded (in EXPAND)	Time of interferon therapy is not recorded (in EXPAND)	Interferon users excluded (in EXPAND)
No Recent Relapse in Specified Time-Frame	Not matched	Not matched	Not matched	Matched (≥3 months)	Not matched
	Narrower criteria <3 months (in EXPAND)	NR	Narrower criteria <3 months (in EXPAND)	Removed patients with most recent relapse within 3 months (in EXPAND)	NR
Documented Progression in Specified Time-Frame	Matched	Matched	Matched	Not matched (prior year)	Not matched (prior 1 year)
	Similar criteria (6-month progression in the past 2 years)	Similar criteria (progressive deterioration for ≥6 months within 24 months)	Similar criteria (progression in prior 24 months)	Time since disability progression was not captured (in EXPAND)	Time since disability progression was not captured(in EXPAND)
Duration of MS	Not matched	Matched (≥2)	Not matched	Not matched	Not matched
	NR	Removed patients with MS duration <2 years (in EXPAND)	NR	NR	NR
Duration of SPMS	Not matched	Not matched	Matched (≥6 months	Matched (≥2 years)	Not matched
	NR	NR	Removed patients with SPMS for <6 months (in EXPAND)	Removed patients with SPMS onset <2 years (in EXPAND)	NR
MS Severity Score	Not matched	Not matched	Not matched	Matched (≥4)	Not matched
	NR	NR	NR	Removed patients with MS severity score of <4 (in EXPAND)	NR
T25FW Test Score	Not matched	Not matched	Not matched	Matched (≤30 s)	Not matched
	NR	NR	NR	Removed patients with timed T25FW >30 s	NR

EDSS=expanded disability status scale; IFN= interferon; MS= multiple sclerosis; SPMS=secondary progressive multiple sclerosis; T25FW= timed 25-foot walk test; NR=not reported; s=seconds

During clarification (A21b), the company provided Table 6 (copied below as Table 22), which shows the similarities and differences between EXPAND and the comparator trial baseline populations as rated by the company.

Table 22. Baseline characteristics in EXPAND and comparator trials

Baseline Patient Characteristics	SPMS					
	EXPAND	ASCEND	North American	IMPACT	European Study	SPECTRIMS
Age (mean years)	48	47.2	46.8	47.6	41	42.8
Proportion female (%)	60	62	63	64	61	63
Mean EDSS score	5.4	5.6	5.1	5.2	5.1	5.4
Proportion of patients with EDSS score ≥6.0 (%)	56	63	NR	48	45	NR
Time since onset of MS symptoms (mean years)	16.8	16.5	NR	NR	NR	NR
Duration of MS (mean years)	12.6	12.1	14.7	16.5	13.1	13.3
Duration of SPMS (mean years)	3.8	4.8	4	NR	2.2	4
Normalised brain volume (mean cm3)	1423	1423	NR	NR	NR	NR
Proportion of patients with Gd+ lesions of T1-weighted images (%)	21	24	NR	36	NR	NR
Total volume of T2 lesions on T2-weighted images (mean mm3)	15,321	16,793	NR	NR	NR	NR
Proportion of patients without previous use of a DMT (%)	22	23**	NR	NR	NR	NR
Proportion of patients without previous IFN use (%)	37.1	NR	100*	100*	100‡	100*
Mean Timed 25-Foot Walk Test (seconds)	16.7	11.2***	NR	14.5	NR	NR
Time since most recent relapse (months)	59	57	NR	44.4	NR	NR
Proportion of patients relapse-free in prior year (%)	78	84	NR	61	NR	NR
Proportion of patients relapse-free in prior 2 years (%)	64	71	55	NR	30	53
Number of relapses per patient in the prior year (mean)	0.2	NR	NR	0.6	NR	NR
Number of relapses per patient in the previous 2 years (mean)	0.7	NR	0.8	NR	NR	0.9

Green = the characteristic is ≤10% different from that in EXPAND; Red = the characteristic is >10% different from that in EXPAND.
Abbreviations: DMT: disease-modifying therapy; EDSS: expanded disability status scale; IFN: interferon; MS: multiple sclerosis; SPMS: secondary progressive multiple sclerosis.

The ERG note that matching alone to each comparator trial produced a large drop in sample size of the EXPAND[2] IPD (CS Appendix D; Tables 49-59, pages 118-140) (see Section 4.3.3.3), from 1645 patients included in the analysis to [redacted] in scenario A (company base-case). The reduction of such magnitude in the sample size suggests substantial heterogeneity in the inclusion/exclusion criteria of SPMS patients across the EXPAND[2] study and the other five trials included in the MAIC. For example, the matching to SPECTRIMS study resulted in a drop of the EXPAND[2] IPD sample size from [redacted] to the ESS of [redacted] patients (based on matched but unadjusted analysis). The ERG are concerned with the large drop in ESS for some of the MAIC analyses, for example the comparison between EXPAND and IMPACT had an ESS of [redacted] for the time to 3-month CDP outcome. During clarification, the ERG requested "*a*

summary of the EXPAND study participants who were excluded on the basis of the matching done in the MAIC" (clarification question A21c). The company provided clarification Table 7 (Table 23), which presents the number of total patients excluded after matching.

Table 23. Baseline characteristics of patients in the EXPAND study excluded during the matching conducted in the MAIC

Summary of patients excluded after matching	**EXPAND matched to study:**					
	SPECTRIMS [5, 6]	**North American study[7]**	**European study[8, 9]**	**Pooled NA & EU Studies[7-9]**	**IMPACT [10]**	**ASCEND[4]**
Clinical endpoint of interest	Time to 3-month CDP; ARR	Time to 6-month CDP	Time to 3-month CDP	ARR	Time to 3-month CDP; ARR	Proportion 6-month CDP; ARR
Number of **total** patients excluded after matching, N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of **siponimod-treated** patients excluded after matching, N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NA=North American; EU=European; IFN=interferon; TIW=three times a week; Q2D=once every two days; Q4W=once every 4 weeks; QW=once weekly; MS=multiple sclerosis; SPMS=secondary progressive multiple sclerosis T25FW= timed 25-foot walk test						

The company was unable to match the EXPAND[2] study (siponimod group) IPD to the other five trials comparator treatment groups matching factors included in Table 24.

Table 24. Factors on which the EXPAND2 study IPD (siponimod) and other trials (comparator treatment groups) could not be matched

Study	Comparator treatment	Matching factors
SPECTRIMS study[5, 6]	Interferon β 1a (22 µg /44 µg TIW)	- No recent relapse in specified time frame - Duration of MS - Duration of SPMS - MS severity score - T25FW test score
IMPACT study[10]	Interferon β 1a (60 µg QW)	- No recent relapse in specified time frame - Documented progression in specified - Duration of MS - Duration of SPMS - MS severity score - T25FW test score
NA study[7]	Interferon β 1b (250 µg Q2D)	-Age - No recent relapse in specified time frame - Duration of SPMS - MS severity score - T25FW test score
EU study[8, 9]	Interferon β 1b (250 µg Q2D)	- No recent relapse in specified time frame - Duration of MS - MS severity score - T25FW test score
ASCEND study)[4]	Natalizumab (300 mg Q4W)	- Prior IFN therapy - Documented progression in specified

Study	Comparator treatment	Matching factors
		time frame - Duration of MS
NA=North American; EU=European; IFN=interferon; TIW=three times a week; Q2D=once every two days; Q4W=once every 4 weeks; QW=once weekly; MS=multiple sclerosis; SPMS=secondary progressive multiple sclerosis T25FW= timed 25-foot walk test		

4.3.3.2 Adjustment results

The company was able to adjust the EXPAND trial IPD for some, but not all the pre-defined EM between the EXPAND IPD (siponimod group) and the aggregate-level data from the five trials (comparator treatment groups) (CS Appendix D; Tables 49-59, pages 117-140), see Table 25. For example, adjustments for comparisons of siponimod versus interferon β-1a (SPECTRIMS)[6] or interferon β-1b (NA and EU studies)[8, 9, 31] for the effects on CPD were not possible for a) normalised brain volume, b) gadolinium-enhancing lesions on T1-weighted images, and c) total volume of T2 lesions on T2-weighted images. These factors were not reported in the publications of these trials. Likewise, the comparisons between siponimod versus interferon β-1b (EU study),[8, 9] natalizumab (ASCEND)[4] or interferon β-1a (IMPACT)[10] could not be adjusted for the number of relapses in prior two years given the absence of data in the study publications.

The comparisons between siponimod and other treatments (interferon β-1a, interferon β-1b) for the effects on ARR could not be adjusted for a) time since onset of most recent relapse, b) number of relapses per patient in one year prior to study, and c) total volume of lesions on T2-weighted images. The comparison between EXPAND)[2] (siponimod group) and interferon β-1b (250 µg Q2D; (from NA and EU studies)[8, 9, 60] on ARR could not be adjusted for any of the five pre-selected factors (Table 26).

Table 25. Matching and adjustment results in MAIC (change in distribution of effect modifiers): siponimod vs. comparative treatment for confirmed progression in disability (CPD)

Study ID	Effective sample size (N, [%])	Age (mean, SD)	EDSS score at screening (mean, SD)	Duration of MS (in years) since diagnosis (mean, SD)	Normalised brain volume (mm^3) mean, SD	Gadolinium-enhancing lesions on T1-weighted images (%)	Duration of SPMS (mean, SD)	Total volume of T2 lesions on T2-weighted images (mm^3) (mean, SD)	Number of relapses in prior 2 years (or any other relapse variable) (mean, SD)	Sex (%)
Siponimod vs. interferon β 1a (22 µg TIW)										
SPECTRIMS [5, 6]	618	42.8 (7.1)	5.4 (1.1)	13.3 (7.1)	NR	NR	4 (3)	NR	0.9 (1.3)	63.0
EXPAND (unmatched) [2]	[redacted]									
EXPAND[2] (matched unadjusted)	[redacted]									
Scenario A	[redacted]									
Siponimod vs. interferon β 1a (44 µg TIW)										
SPECTRIMS [5, 6]	618	42.8 (7.1)	5.4 (1.1)	**13.3** (7.1)	NR	NR	4 (3)	NR	0.9 (1.3)	63.0
EXPAND (unmatched) [2]	[redacted]									
EXPAND[2] (matched unadjusted)	[redacted]									
Scenario A	[redacted]									
Siponimod vs. interferon β 1b (250 µg Q2D)										
NA Study [7]	939	46.83 (8.14)	5.13 (1.18)	14.66 (8.32)	NR	NR	4.03 (3.48)	NR	0.83 (1.32)	62.6
EXPAND[2] (unmatched)	[redacted]									
EXPAND[2] (matched unadjusted)	[redacted]									
Scenario A	[redacted]									
EU Study [8, 9]	718	41 (7.2)	5.15 (1.1)	13.1 (7.06)	NR	NR	2.15 (2.3)	NR	NR	61.1
EXPAND[2] (unmatched)	[redacted]									

EXPAND (matched unadjusted)	[redacted]									
Scenario A	[redacted]									
Siponimod vs. Natalizumab (300 mg Q4W)										
ASCEND[4]	887	47.25 (7.61)	5.6 (0.9)	12.14 (6.88)	1423.37 (82.95)	76.2	4.8 (3.37)	16793 (17003)	NR	62.0
EXPAND (unmatched) [2]	[redacted]									
EXPAND (matched unadjusted)	[redacted]									
Scenario A	[redacted]									
Siponimod vs. interferon β 1a (60 µg QW)										
IMPACT[10]	436	47.55 (7.95)	5.2 (1.1)	16.45 (9)	NR	16.5	NR	NR	NR	64
EXPAND (unmatched) [2]	[redacted]									
EXPAND (matched unadjusted)	[redacted]									
Scenario A	[redacted]									

interferon β=interferon beta; TIW=three times weekly; Q2D=every other day; DMT=disease-modifying therapy; once every 4 weeks; QW=once weekly; NAD=not adjusted; NR=not reported

Table 26. Matching and adjustment results in MAIC (change in distribution of effect modifiers): siponimod vs. comparative treatment for annualised relapse rate (ARR)

Study ID	Effective sample size	Time since onset of most recent relapse	Number of relapses per patient in one year prior to study	Number of relapses per patient in two years prior to study	Gadolinium-enhancing lesions on T1-Weighted images	Total volume of lesions on T2-weighted images
Siponimod vs. interferon β 1a (22 µg TIW)						
SPECTRIMS [5, 6]	616	NR	NR	0.9 (1.3)	NR	NR
EXPAND (unmatched) [2]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EXPAND (matched unadjusted)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario A	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Siponimod vs. interferon β 1a (44 µg TIW)						
SPECTRIMS [5, 6]	616	NR	NR	0.9 (1.3)	NR	NR
EXPAND (unmatched) [2]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EXPAND (matched unadjusted)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario A	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Siponimod vs. interferon β 1b (250 µg Q2D)						
NA and EU Studies [8, 9, 60]	1343	NR	NR	NR	NR	NR
EXPAND (unmatched) [2]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EXPAND (matched unadjusted)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario A	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Siponimod vs. Natalizumab (300 mg Q4W)						
ASCEND [4]	887	4.75 (4.25)	NR	NR	76.2	16793.21 (17003.8)
EXPAND (unmatched) [2]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EXPAND (matched unadjusted)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario A	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Siponimod vs. interferon β 1a (60 µg QW)						
IMPACT[10]	436	3.7 (5.1)	0.55 (1.0)	NR	16.5	NR
EXPAND (unmatched) [2]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EXPAND (matched unadjusted)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario A	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NAD=not adjusted; NR=not reported						

4.3.3.3 Effective sample size

The company report that matching the EXPAND[2] trial IPD to each comparator trial reduced the ESS to approximately [redacted] (CS Document B, page 78). The ERG consider that the approach to matching satisfactory, however we are concerned that the ESS represents a substantial drop from the actual sample size of EXPAND (1651 patients randomised).[2] The company acknowledge that this difference illustrates the magnitude of the dissimilarity between the inclusion criteria between the comparator trials and EXPAND[2], and note that the ESS is not miniscule compared to the comparator trials.

The ERG note that the reported ESS of approximately [redacted] for the matching and unadjusted population was not the same as the ESS used in the company base-case. On page 16 of the clarification responses (A19), the company provided the ERG with *"...the distributions of adjustment weights of Scenario A (i.e., base case; fully matched and adjusted)*". The ERG checked the ESS for the matching process, as documented in CS Appendix D.1.6 (Tables 49-59), and noted that Scenario A has an ESS outside the stated range of [redacted] of the EXPAND ITT, some ESS are very small (see Table 25 and Table 26).

The ERG consider the range used in the economic base-case ESS to be [redacted] as stated in clarification response A19. The ERG note that when the ESS is markedly reduced, estimates become unstable and inferences depend heavily on a small number of individuals, due to a lack of population overlap (see Section 794.3.3.1).

4.3.3.4 Distribution of adjustment weights

During clarification the ERG requested that the company provide "the distribution of regression-based weights/propensity scores used in the MAIC" (A19). The company provided the distributions of adjustments weights for siponimod (from EXPAND) against the comparator studies which the ERG have summarised in as a spread of weights in Table 27.

The ERG note that the weights are generally positively skewed, and both the mean and median is less than one. The ERG suggest that patients who were weighted highly could be removed from the MAIC analysis as a sensitivity analysis (SA). However, this SA was not performed by the company or the ERG, as it was not possible without the IPD from the EXPAND trial which was not provided in the CS or as part of the clarification.

Table 27. Summary of the distribution of adjustment weights used in the MAIC

Comparator study	Outcome	Min	Median	Mean	Max
SPECTRIMS[5, 6]	Time to 3-month CDP	[redacted]	[redacted]	[redacted]	[redacted]
North American Study[7]	Time to 6-month CDP	[redacted]	[redacted]	[redacted]	[redacted]
European Study[8, 9]	Time to 3-month CDP	[redacted]	[redacted]	[redacted]	[redacted]
ASCEND[4]	Time to 6-month CDP	[redacted]	[redacted]	[redacted]	[redacted]
IMPACT[10]	Time to 3-month CDP	[redacted]	[redacted]	[redacted]	[redacted]
SPECTRIMS[5, 6]	ARR	[redacted]	[redacted]	[redacted]	[redacted]
ASCEND[4]	ARR	[redacted]	[redacted]	[redacted]	[redacted]
IMPACT[10]	ARR	[redacted]	[redacted]	[redacted]	[redacted]

4.3.4 MAIC analysis results (efficacy): indirect effect estimates for outcomes of interest

The MAIC analysis results and efficacy estimates for siponimod versus other comparator treatments for time to 3- and 6-month CDP and ARR are provided in Table 28 and Table 29, respectively.

4.3.4.1 Confirmed disability progression (CDP) - ITT population

Time to 3-month CDP

The results of MAIC analysis indicated that the use of siponimod compared to interferon β-1a (IM; 60µg once a week) was associated with a significant [redacted] in disability progression measured by the time to 3-month CDP ([redacted]) (Table 28). In contrast, this difference was [redacted] when siponimod was compared to interferon β-1a (SC) administered 3 times a week either at 22µg ([redacted]) or 44µg ([redacted]). Likewise, siponimod was [redacted] different from interferon β-1b (SC 250 µg) administered once every other day ([redacted]).

Time to 6-month CDP

Siponimod was shown to significantly [redacted] the disability progression (time to 6-month CDP) compared to interferon β-1b (SC 250 µg) administered once every other day ([redacted]) (Table 28).

Patients with 6-month CDP

The proportion of patients with 6-month CDP was [redacted] different between siponimod and natalizumab ([redacted]). The ERG note that time to 6-month CDP for this comparison could not be calculated owing to differences in the outcome definition across EXPAND[2] and ASCEND[4] studies. Instead for both studies, the company calculated the proportion of patients who experienced 6-month CDP by 96 weeks based on an increase in EDSS (Table 28).

4.3.4.2 Annualized relapse rate (ARR) - ITT population

The ARR was significantly [redacted] with siponimod compared to interferon β-1a (SC 22µg/44µg) ([redacted]). The effect of siponimod on the ARR was [redacted] different from that of interferon β-1a IM 60µg ([redacted]), interferon β-1b SC 250µg ([redacted]), and natalizumab IV 300mg ([redacted]) (Table 29).

Table 28. Summary of MAIC effect estimates for 3- and 6-month confirmed disability progression (CDP)

Comparator treatment (study name)	Treatment regimen	Effect estimates HR (95% CIs) from individual studies		Sample size			MAIC effect estimates HR (95% CIs) [β] Siponimod vs. comparator	MAIC effect estimates HR (95% CIs) [β] Siponimod vs. placebo
		Comparator study (comparator vs. PL)	EXPAND study[2] (siponimod vs. PL)	Comparator study	EXPAND study[2]*	ESS[β]		
Time to 3-month CDP								
Interferon β-1a (SPECTRIMS study)[5, 6]	SC 22 µg TIW	0.88 (0.69, 1.12)	0.79 (0.65, 0.95)	618	[redacted]	[redacted]	[redacted]	[redacted]
	SC 44 µg TIW	0.83 (0.65, 1.07)					[redacted]	
Interferon β-1b (EU study)[8, 9]	SC 250 µg Q2D	0.74 (0.60, 0.91)		718	[redacted]	[redacted]	[redacted]	[redacted]
Interferon β-1a (IMPACT study)[10]	IM 60 µg QW	0.98 (0.68, 1.41)		436	[redacted]	[redacted]	[redacted]	[redacted]
Time to 6-month CDP								
IFNβ-1b (NA study)[7]	SC 250 µg Q2D	0.92 (0.71, 1.20)	0.74 (0.60, 0.92)	939	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of patients with 6-month CDP (96 weeks) [µ]								
Natalizumab (ASCEND study)[4]	IV 300 mg Q4W	1.06 (0.74, 1.53)	[redacted]	887	[redacted]	[redacted]	[redacted]	[redacted]

ESS=effective sample size; CI=confidence interval; CDP=confirmed disability progression; HR=hazard rate ratio; TIW=three times weekly; EU=European study; NA= North American Study; QW=once weekly; Q2D=once every other day; 9-HPT=9-hole peg test; T25FW=timed 25-foot walk; SC=subcutaneous; IV=intravenous; IM=intramuscular

*Pre-matched/adjusted sample size.

[β] ESS and MAIC effect estimates refer to scenario A (matched and adjusted for all available ranked effect modifiers/baseline patient characteristics).

[µ] Odds ratio (OR) for patients who experienced 6-month CDP by 96 weeks based on an increase in EDSS alone was calculated for both studies. For EXPAND study, the proportion of patients with this outcome was calculated using the IPD, based on a conservative assumption that all patients censored at or before 96 weeks had experienced a 6-month CDP event. The studies could not be compared for the time to 6-month CDP, because this outcome in ASCEND study was defined as an increase in any of the scores of EDSS, T25FW, and 9-HPT, whereas in EXPAND study, the CDP was defined as an increase in EDSS only.

Table 29. Summary of MAIC effect estimates for annualised relapse rate (ARR)

Comparator treatment (study name)	**Treatment regimen**	**Effect estimates RR (95% CIs) from individual studies**		**Sample size**			**MAIC effect estimates RR (95% CIs)[β] Siponimod vs. comparator**	**MAIC effect estimates RR (95% CIs)[β] Siponimod vs. placebo**
		Comparator study (comparator vs. PL)	EXPAND study[2] (siponimod vs. PL)	Comparator study	EXPAND study[2]*	ESS[β]		
Interferon β-1a (SPECTRIMS study)[5, 6]	SC 22 µg TIW	0.69 (0.56, 0.84)	0.45 (0.34, 0.59)	616	[redacted]	[redacted]	[redacted]	[redacted]
	SC 44 µg TIW	0.69 (0.56, 0.85)			[redacted]		[redacted]	
Interferon β-1b (EU study)[8, 9] (NA study)[7]	SC 250 µg Q2D	0.65 (0.48, 0.88)		1,343	[redacted]	[redacted]	[redacted]	[redacted]
Interferon β-1a (IMPACT study)[10]	IM 60 µg QW	0.67 (0.49, 0.90)		436	[redacted]	[redacted]	[redacted]	[redacted]
Natalizumab (ASCEND study)[4]	IV 300 mg Q4W	0.45 (0.32, 0.63)		887	[redacted]	[redacted]	[redacted]	[redacted]

ESS=effective sample size; CI=confidence interval; ARR= for annualised relapse rate; RR=Rate ratio; TIW=three times weekly; EU=European study; NA= North American Study; QW=once weekly; Q2D=once every other day; 9-HPT=9-hole peg test; T25FW=timed 25-foot walk; SC=subcutaneous; IV=intravenous; IM=intramuscular

*Pre-matched/adjusted sample size.

[β] ESS and MAIC effect estimates refer to scenario A (matched and adjusted for all available ranked effect modifiers/baseline patient characteristics).

[µ] Matched only (no scenario A).

4.4 Critique of the indirect comparison and/or multiple treatment comparison

4.4.1 Summary of the MAIC

In the absence of head-to-head RCT evidence comparing siponimod to other active treatments, the company examined the feasibility of aggregate data-based standard methods for indirect comparisons (e.g., NMA) following to the guidance of the NICE DSU TSD[57] and concluded that such analysis was not feasible due to substantial cross-trial differences in study populations and outcome definitions. The company conducted a placebo anchored MAIC analysis to compare siponimod to other active treatments used in patients with SPMS in the UK with respect to disability progression, relapse rates, and disease MRI-based activity.

The company MAIC was based on the IPD from the EXPAND study[2] and the aggregate published data from five comparator treatment trials of natalizumab (ASCEND),[4] interferon beta-1b (EU study, NA study),[7-9] and interferon beta-1a (SPECTRIMS, IMPACT).[5, 6, 10] The company argued that a MAIC using IPD from the EXPAND[2] study would allow them to match the trial populations and adjust effect estimates for *a priori* determined EM by producing more valid effect estimates than a standard indirect method (e.g., placebo-anchored NMA). In an anchored MAIC, it is important to adjust for all treatment EM to ensure balance and reduce bias, but not to adjust for purely prognostic variables so as to avoid inflating standard error due to over-matching.

The company identified and ranked treatment EM through a combination of clinical opinion and data-driven analysis of the EXPAND IPD[2]. The analysis to identify EM involved univariate regression analysis of the baseline characteristics in EXPAND.[2] This, along with univariate exploration of early MAIC results and the clinician-ranked lists, informed the EM in the MAIC. The ERG note that the company did not report any results of the univariate regression analysis on ARR, or evidence that they were performed.

The results from the matched and adjusted analyses (ITT population) suggested that the use of siponimod was associated with a significantly [redacted] time to 3-month CDP compared to IM-interferon β-1a and [redacted] time to 6-month CDP compared to SC- interferon β-1b. Moreover, siponimod showed a significantly [redacted] ARR compared with SC-interferon β-1a. The remaining effect estimates of MAIC between siponimod and all other comparator treatments were [redacted].

4.4.1.1 ERG NMA

The ERG consider that the feasibility assessment for NMA and the justification for conducting the MAIC analysis provided in the CS were not adequate (Section 4.3.1.1). The company used 10% limit and SMD=0.1 threshold to operationalise their decisions when comparing baseline characteristics across the studies. The impact of the decisions based on these arbitrary rather than empirically-based thresholds is difficult to determine. Therefore, we conducted an independent assessment of the comparability of the five study populations, outcome definitions and EXPAND[2] trial effect modifiers to inform our exploratory NMAs (Section 4.5).

The ERG are concerned by the dichotomisation of continuous variables used by the company in the matching process for the MAIC (3 groups for the number of relapses in prior 2 years), resulting in a potential large loss of information. The ERG understands that this may have been done to limit the number of categories thus increasing the ESS, but this assumes an equal effect of patients in these groups. For example, a 42 year old and a 60 year old are assumed to be equal, however the ERG highlight that disability progression may be considerably different in these individuals. The treatment EM have been selected based on their influence on disability progression.

4.4.2 Points of uncertainty

The ERG consider that the results of MAIC analysis presented in the CS should be viewed with caution due to the following issues:

- The observed cross-trial heterogeneity in inclusion/exclusion criteria, EM and outcome definitions
- The inability to match the populations for important study inclusion/exclusion criteria (e.g., prior interferon β therapy, age, duration of MS/SPMS, MS severity score, history of recent relapse) is also an issue:
    - The EXPAND IPD and the ASCEND study could not be matched for time to 6-month CDP because of the difference in the outcome definition across the two trials. Specifically, this outcome in ASCEND study was defined as an increase in any of the scores of EDSS, T25FW, and 9-HPT, whereas in EXPAND, CDP was defined as an increase in EDSS only. Therefore, instead of the time to 6-month CDP, the company determined for both studies the proportion of patients who experienced 6-month CDP by 96 weeks based on an increase in EDSS alone (CS

Appendix D, page 105). The ERG note that the proportion-based outcome that the company presented may not be an accurate representation of the time to 6-month CDP outcome

- The inability to adjust for a number of *a priori* defined EM (e.g., normalised brain volume, gadolinium-enhancing lesions, total volume of T2 lesions, the number of relapses in prior 2 years, time since onset of most recent relapse, number of relapses per patient in one year prior to study)
- The company could not match and adjust to account for imbalances in one or more unknown EM. Even though the RoB in the studies included in MAIC was judged to be low for most of the domains, this would not remedy the bias in the MAIC estimates that may have resulted from inability to control for confounding through matching and adjustment
- The substantial reduction in ESS for all comparisons across the matched-adjusted data compared to pre-matched/adjusted sample size ([redacted], indicates a great extent of non-overlap/dissimilarity in inclusion criteria, baseline population characteristics, outcomes definitions, and reporting comprehensiveness between the trials included in MAIC
    - The ERG consider the ESS included in the economic base-case to be between [redacted]XXX The ERG note that when the ESS is markedly reduced, confidence internals are wide, effect estimates become unstable and inferences depend heavily on a small number of individuals, due to a lack of population overlap[57]
- The visual inspection of distribution plots of weights (provided by the company in the clarification response A19) used in the MAIC adjustments confirmed the existence of variation and extreme values across both treatments and outcomes. The ERG note that most of the MAIC effect estimates for disability progression and relapse rates were statistically non-significant with sufficiently wide 95% CIs to include effects compatible with both the superiority and inferiority of siponimod over the comparator treatment, thereby rendering these estimates inconclusive.

4.4.2.1 Further considerations

The ERG were unable to check the MAIC analysis included in the CS as the IPD was not provided by the company. The ERG requested the EXPAND IPD and R codes for the MAIC

during clarification (B2), however we were only provided with the relevant R codes. Thus, the ERG were unable to replicate or assess the MAIC analysis performed by the company.

The ERG consider that the relevance of comparator treatment and generalisability of results from the population of the comparator treatment trial to the target population should be considered with caution. The target population for siponimod was defined as adult patients with SPMS (see Section 3.1). Current therapies indicated for relapsing forms of MS are not recommended for the treatment of non-relapsing SPMS (non-active form) due to their lack of efficacy shown in several RCT that included predominantly patients with non-relapsing SPMS (>50%).[4-7, 10] Therefore, the MAIC estimates based on the comparator treatments from these trials would have very limited use.

The ERG note that in clarification response A21b , the company state that "*the disease course of MS forms a spectrum; implementation of the definition of SPMS in UK clinical practice varies widely, making the generalisability to the English SPMS population relatively difficult to ascertain*". The response continues "*when considering the generalisability [of the results of the MAIC] to the English SPMS population, all the trials include patients diagnosed with MS according to criteria that are used in the UK. The lack of clarity on the definition of SPMS is reflected in the differences in the different trial populations: although differences exist, all are generalisable to somewhere on the spectrum of SPMS diagnosis*".

Of the five comparator treatment trials included in MAIC, one trial of interferon-β 1b[8, 9] had approximately 70% patients with relapsing SPMS (active form). The ERG consider this to be the population most similar to the target population defined above. Interferon-β 1b is recommended as a treatment option for SPMS patients with active disease.[37] Therefore, the MAIC effect estimate for siponimod compared to interferon-β 1b on time to 3-month CDP ([redacted]) would be the most relevant to the NICE final scope (see Section 3.3).

However, the ERG note that the interferon-β 1b trial (EU study[8, 9]) contains a contains a historic population sample as the studies were published in 1998[8] and 2001[9], therefore considerably older than the more recent EXPAND study which was published in 2018.[2] The SPMS patients in the EU study are expected to be different in important EM from patients with SPMS in the current clinical practice. The criteria for definition and classification of SPMS has evolved overtime and varies widely in practice due to the lack of precise clinical, imaging or pathologic criteria for the

diagnosis of SPMS along the MS continuum,[61, 62] Therefore, the ERG consider that the assumption of shared EM would be violated in terms of generalising the MAIC result to the target population in the context of current clinical practice.[57] Similar limitations may apply to the effect estimate of the MAIC comparison (for time to 3-month CDP and ARR) based on the SPECTRIMS study, whose reports were published in 2001.[5, 6]

Besides methodological shortcomings inherent to MAIC, the evidence itself was limited because of the absence of head-to-head trials comparing siponimod to other therapies, insufficient number of comparator treatment trials conducted in people with SPMS, lack of evidence for UK patients to generalise trial results, and no efficacy and safety data in people with non-relapsing form of SPMS. In addition:

- The MAIC analysis was based on ITT populations only and a subgroup analysis (e.g., by active relapsing form of SPMS) was not feasible
- The MAIC analysis did not include comparative safety assessment between siponimod and other comparator treatments.

4.4.3 Summary

In conclusion, the evidence from MAIC analysis is limited and should be interpreted with caution, particularly in terms of unaccounted cross-trial heterogeneity in the characteristics of the populations and small ESS. These methodological shortcomings coupled with gaps in evidence and inconsistent reporting render most of the MAIC findings inconclusive. The ERG, suggest that it is problematic to draw definitive conclusions regarding the comparative efficacy of siponimod in relation to other treatments used in patients diagnosed with SPMS.

4.5 Additional work on clinical effectiveness undertaken by the ERG

As described in Section 4.4 the ERG conducted exploratory NMAs for 6-month CDP, 3-month CDP and ARR outcomes using aggregate data from the EXPAND trial and the five included comparator studies (SPECTRIMS,[5, 6] NA Study,[7] EU Study,[8, 9] ASCEND,[4] and IMPACT).[10] During clarification (A18), the ERG requested the EXPAND IPD and R codes used in the MAIC, however we were only provided with the relevant R codes as the company state that they were "*uncertain whether Novartis has adequate permissions to share the requested EXPAND IPD with an external party*". Thus, the ERG were unable to replicate the MAIC analysis carried out by the

company. The ERG were also unable to assess the trial populations after the MAIC matching and adjustment had taken place as the Kaplan–Meier plots for these populations were not included in the CS.

4.5.1 Summary of included studies

For completeness the ERG present the intervention versus placebo published effect estimates for the key outcomes (3 and 6-month CDP) across the six included studies in Table 30. The data suggest favourable results for all the inventions listed in Table 30, only siponimod (6-month CDP HR 0.74, 95% CI:, 0.60, 0.92, proportion with 6-month CDP [96w], 3-month CDP HR 0.79 95% CI:, 0.65, 0.97) and interferon- β-1b (3-month CDP HR 0.74 95% CI, 0.60, 0.91) demonstrated significantly different results when compared to placebo. The comparisons for ARR (Table 31) all demonstrated significantly different results for intervention compared to placebo.

Table 30.Summary of published effectiveness estimates: invention vs. placebo (CS Document B , Table 41)

Study	Intervention	Comparator	Hazard ratio	95% CI	
Time to 6-month CDP (key effectiveness estimate in the base case of the economic model)					
EXPAND[2]	Siponimod	Placebo	**0.74**	**0.60**	**0.92**
NA Study[7]	Interferon β-1b	Placebo	0.92[a]	0.71	1.20
Proportion with 6-month CDP (96w) [b]					
EXPAND[2]	Siponimod	Placebo	[redacted]	[redacted]	[redacted]
ASCEND[4]	Natalizumab	Placebo	1.06 [b] (OR)	0.74	1.53
Time to 3-month CDP (EXPAND primary outcome)					
EXPAND[2]	Siponimod	Placebo	**0.79**	**0.65**	**0.95**
SPECTRIMS[5, 6]	Interferon β-1a 22 (μg)	Placebo	0.88 [a]	0.69	1.12
	Interferon β-1a 44 (μg)	Placebo	0.83	0.65	1.07
EU Study[8, 9]	Interferon β-1b	Placebo	**0.74** [a]	**0.60**	**0.91**
IMPACT[10]	Interferon β-1a 60 (μg)	Placebo	0.977	0.68	1.41

[a] The HR and/or CI were not reported in the publication. Missing values were estimated using either the reported HR and p-value, the reported Kaplan-Meier curve through curve-fitting, or through analysis of IPD, as appropriate.

[b] The proportion of patients who experienced 6-month CDP by 96 weeks based on an increase in EDSS alone. For EXPAND, the proportion of patients with this outcome was calculated using the IPD, based on a conservative assumption that all patients censored at or before 96 weeks had experienced a 6-month CDP event. BOLD = significant difference

Table 31. Summary of published ARR estimates: intervention vs. placebo (CS Document B , Table 42)

Study	Intervention	Comparator	Rate ratio	95% CI	
ARR					
EXPAND[2]	Siponimod	Placebo	**0.45**	**0.34**	**0.59**
NA Study/EU Study[7-9]	Interferon β-1b	Placebo	**0.65**	**0.48**	**0.88**
SPECTRIMS[5, 6]	Interferon β-1a 22 (μg)	Placebo	**0.69**	**0.56**	**0.84**
	Interferon β-1a 44 (μg)	Placebo	**0.69**	**0.56**	**0.84**
ASCEND[4]	Natalizumab	Placebo	**0.453**	**0.32**	**0.63**
IMPACT[10]	Interferon β-1a 60 (μg)	Placebo	**0.67**	**0.49**	**0.90**

BOLD = significant difference

To undertake exploratory NMA we used the package *'network'* in Stata 15.[63] We did not perform sensitivity analyses on different prior distributions as this package operates in the frequentist paradigm. As the networks for each of CDP outcomes were sparse, we used a fixed-effects model. For ARR, the random-effects model did not converge, so a fixed-effects NMA was also conducted.

4.5.2 The EXPAND study versus the North American Study (6-month CDP)

In order to perform the NMA for 6-month CDP, we compared the two studies included for 6-month CDP outcome (EXPAND[2] and NA study[7]) (Table 30). The two studies had some differences (as outlined by the company is Appendix D, Table 25 - Table 30 page 92-98).

In summary, the NA study was a three-year RCT evaluating the efficacy and safety of two doses (250 μg and 160 μg/m^2) of SC interferon β-1b administrated every other day versus placebo, for the treatment of 939 patients with SPMS.[7] The ERG note that the NA study, study design was similar to EXPAND, with the exception of study duration (mean duration follow-up: 998 days 250-μg group, 1013 days 160-μg/m2 group, 1003 days placebo group vs. 3 years, respectively) and method of placebo administration (SC vs. oral, respectively). The inclusion/exclusion criteria of the NA study and EXPAND were similar with the exception of 'previous interferon treatment', which was an exclusion criterion in the NA study. The ERG consider the outcome definitions comparable. Outcome definitions for ARR and discontinuation in the NA Study were identical to EXPAND. Time to 3-month CDP was not reported in the NA Study. The ERG acknowledge that patients were recruited to the NA study between 1997 and 2000 (trial publication date 2004)[7] whereas patients in EXPAND were recruited between 2012 and 2016.[2] The ERG highlight the potential differences in healthcare systems and accompanying clinical practice, in treatment

physiotherapy and standards of care regimes across the time periods. However, these differences are equally problematic for the company MAIC.

The ERG compared the baseline characteristics (the effect modifiers specifically) and outcome measures between the NA study[7] and three groups of EXPAND[2] used in the company MAIC (overall, matched and unmatched populations (see Table 32). Visual inspection across the trials suggest:

- Age appears similar across all groups, the EXPAND matched group is slightly higher but the spread is comparable*
- EDSS score appears similar. It is not clear if a difference between EDSS 5.13 (NA study) and EDSS 5.50 (EXPAND, unmatched) is meaningful
- MS duration is higher in the NA study compared to the groups in EXPAND, although the SD is similar, especially for the EXPAND matched population
- Duration of SPMS appear similar across all groups
- Number of relapses in prior 2 years, appears slightly higher in the NA Study group, although it is not clear if this represents a meaningful difference*
- Proportion female appears similar across groups.

*The ERG note that both 'age' and 'number of relapses in prior 2 years' in the matched EXPAND group differ more from NA study than the EXPAND overall group (after matching, before weighting).

Overall, the ERG do not consider that the matching processes conducted by the company has made a meaningful difference, and it is questionable as to whether it justifies the large reduction in sample size observed in Table 32, i.e., dropping a large number of individuals from the MAIC analysis.

The ERG could not satisfactorily compare outcomes across the two studies, as 6-month CDP outcomes were not reported in the CS for the matched or unmatched MAIC populations. The ERG note that 6-month CDP was not reported in the trial publication for the NA study. The company stated that the definition of disability progression used in the 6-month CDP outcome differed between the studies: "*patients with a baseline EDSS of 5.5 required an increase of 0.5 to qualify as experiencing "progression" in EXPAND, but required an increase of 1.0 in the North*

American Study". The definitions were otherwise identical and were considered to be reasonably equivalent based on clinical opinion. The ERG agree with this assumption.

Table 32 Comparison of effect modifier characteristics and outcome measures between the North American Study and EXPAND (overall, matched, unmatched)

Effect modifiers	**NA Study**	**EXPAND**		
		Overall	**Matched**	**Unmatched**
N	939	[redacted]	[redacted]	[redacted]
Age	46.83 (8.14)	[redacted]	[redacted]	[redacted]
EDSS score at screening	5.13 (1.18)	[redacted]	[redacted]	[redacted]
MS duration since diagnosis	14.66 (8.32)	[redacted]	[redacted]	[redacted]
Duration of SPMS	4.03 (3.48)	[redacted]	[redacted]	[redacted]
Number of relapses in prior 2 years	0.83 (1.32)	[redacted]	[redacted]	[redacted]
Sex (female)	62.60%	[redacted]	[redacted]	[redacted]
Outcome measure				
Time to 6-month CDP				
Intervention	Not reported	218/1096 (19.9%)	Not reported	Not reported
Placebo	Not reported	139/545 (25.5%)	Not reported	Not reported
HR (95% CI)	0.92 (0.71, 1.20)*	0.74 (0.60,0.92)	Not reported	Not reported
P-value	0.61	0.0058	Not reported	Not reported
*HR and CI not reported, only p value. HR and 95% CI were estimated in EXPAND (CS Document B, Table 41 page 76)				

The ERG highlight that the company MAIC excluded 1101 out of a total of 1638 patients in the EXPAND study (Table 32). This represents 67% of the data which have been discarded from the analysis. Discarding a large number of patients in the MAIC analysis is problematic given the similarity in baseline characteristics across the NA study and EXPAND populations in the MAIC.

The ERG consider that typically, increased selection occurs if the populations differ in the matching and decreased selection where the populations are sufficiently similar.

On the basis of the above exploratory assessment, the ERG considers the two populations from the NA study[7] and EXPAND[2] to be sufficiently similar to be pooled together using a fixed effects model indirect comparison (6-month CDP).

The ERG note that the two interventions in the NA study[7] (interferon β-1b) and EXPAND[2] (siponimod) are owned by the company. Therefore, we consider it possible to conduct a valid IPD meta-analysis of the data with appropriate adjustments to account for imbalances across arms. However, the company chose not to do this and instead carried out a MAIC analysis despite the considerable uncertainties and stronger assumptions around such analysis. During clarification (A16) the ERG asked why aggregate data were used, as opposed to IPD from both trials. The company responded: "*Interferon β-1b was developed by Schering AG (now part of Bayer Pharma), and is currently marketed as Betaferon® by Bayer Pharma. Due to a commercial arrangement between the companies, Novartis also markets a brand of interferon β-1b, known as Extavia®.[64] Betaferon and Extavia can be considered the same medicinal product, differing only in brand and commercial terms. Since Novartis did not originally develop interferon β-1b, we do not hold the clinical trial data. Aggregate data were therefore used in the absence of individual patient data (IPD).*"

4.5.3 Time to 6-month CDP exploratory NMA results

The ERG conducted an exploratory fixed effects NMA for time to 6-month CDP outcome using the HR (95% CI) from EXPAND[2] and the NA study.[7] The two interventions are connected via placebo. The numerical data are presented in Table 33 and the network is presented in Figure 4.

Table 33 Data used for time to 6-month CDP ERG NMA

Study	Treatment 1	Treatment 2	Hazard ratio	95% CI	
EXPAND[2]	Siponimod	Placebo	0.74	0.60	0.92
NA Study[7]	Interferon β-1b	Placebo	0.92	0.71	1.20

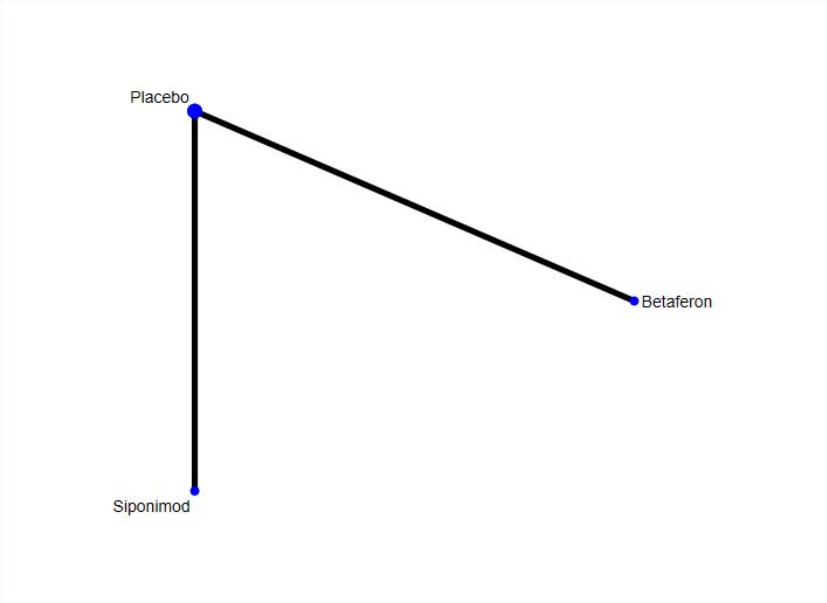


Figure 4 The network of interventions for time to 6-month CDP

The results of ERG NMA for 6-month CDP are presented in Table 34, and are compared to the treatment efficacy results of the company MAIC (CS Document B, Table 41 page 76). In the NMA, siponimod lowers the risk of 6-month CDP compared to the placebo group, but the results are not statistically significant (HR 0.80, 95% CI: 0.57, 1.13).

Table 34. 6-month CDP indirect comparisons CS MAIC vs. ERG NMA

			Siponimod vs Comparator	
Comparator	**Regimen**	**Study**	**Company MAIC HR 95% CI**	**ERG NMA HR 95% CI**
SC interferon β-1b	250 µg Q2D	NA Study	[redacted]	0.80 (0.57, 1.13)

The ERG acknowledge that the network diagram presented in Figure 4 is sparse, therefore consistency cannot be assumed. The ERG also consider that the assumption of transitivity has not been violated as outlined in Section 4.5.2.

4.5.4 ARR exploratory NMA results

The ERG note that univariate regression for ARR was not presented in the CS Appendix section D.1.5. Therefore, a full comparison of the baseline characteristics (effect modifiers) and outcome measures between the studies and the three groups of EXPAND used in the company MAIC was

not possible. The limited characteristics we were able to compare are presented in ERG appendix C Tables 6-10.

The ERG conducted an exploratory fixed effects NMA for ARR outcome using the HR (95% CI) from EXPAND[2] and the five included studies.[4-10] The numerical data used in the NMA are presented in Table 35 and the network is presented in Figure 5. The six interventions are connected via placebo.

Table 35. Data used by the ERG in the NMA: ARR

Study	Treatment 1	Treatment 2	Hazard ratio	95% CI	
EXPAND[2]	Siponimod	Placebo	0.45	0.34	0.59
NA/EU Study[7-9]	SC IFNβ-1b	Placebo	0.65	0.48	0.88
SPECTRIMS[5, 6]	SC IFNβ-1a 22 (μg)	Placebo	0.69	0.56	0.84
	SC IFNβ-1a 44 (μg)	Placebo	0.69	0.56	0.85
ASCEND[4]	Natalizumab	Placebo	0.453	0.32	0.63
IMPACT[10]	IM IFNβ-1a	Placebo	0.67	0.49	0.90

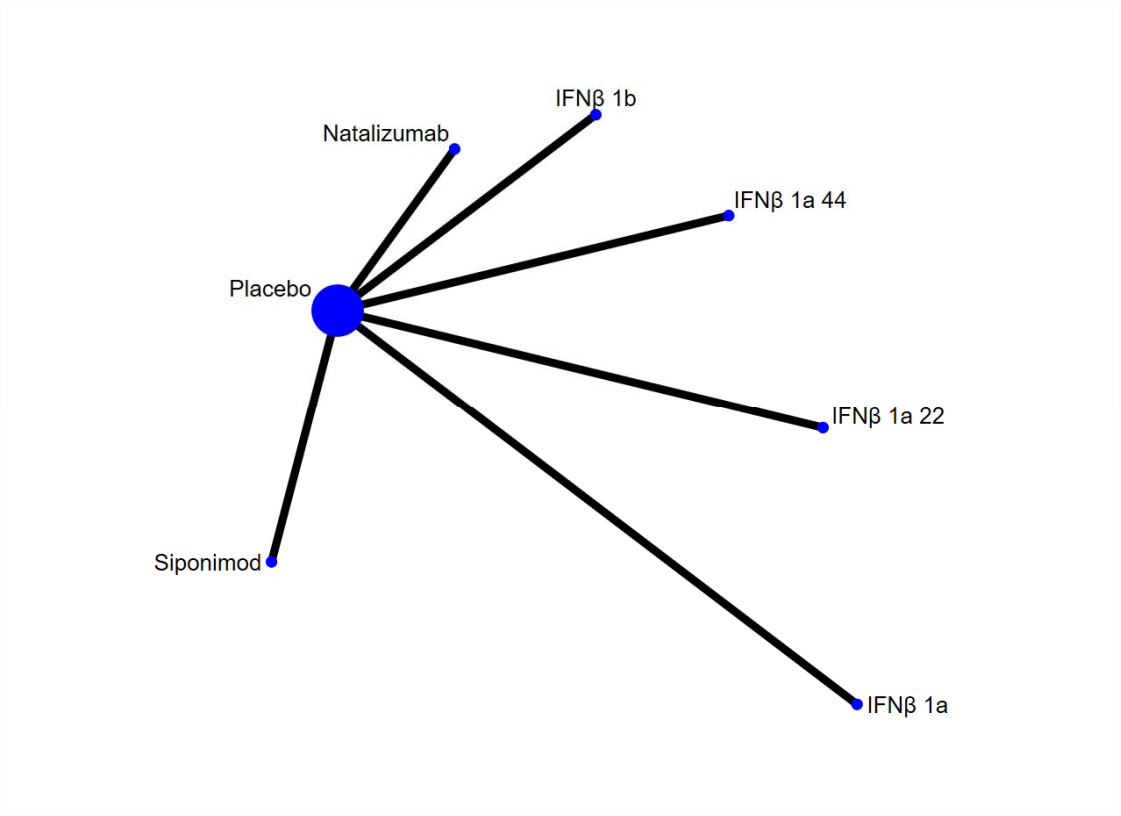


Figure 5. ERG network diagram: ARR

The results of the ERG NMA for ARR are presented in Table 36. We compared the NMA results to the treatment efficacy results from the company MAIC (CS Document B, Table 41 page 76). The results of the NMA differ from the MAIC for all comparisons. Noticeably, in the NMA, siponimod reduces the ARR compared to the placebo group for siponimod versus SC interferon β-1a 22 µg TIW and SC interferon β-1a 44 µg TIW (HR 0.65 95% CI: 0.47, 0.91). All other results in the NMA were not statistically significant.

Table 36. ARR estimates for ITC of siponimod vs. comparator: CS MAIC vs ERG NMA

			Siponimod vs Comparator	
Comparator	**Regimen**	**Study ID**	**Company MAIC HR 95% CI**	**ERG NMA HR 95% CI**
SC interferon β-1a	22 µg TIW	SPECTRIMS[5, 6]	[redacted]	0.65 (0.47, 0.91)
	44 µg TIW	SPECTRIMS[5, 6]	[redacted]	0.65 (0.47, 0.91)
SC interferon β-1b	250 µg Q2D	EU Study[8, 9]	[redacted]	0.65 (0.46, 1.04)
IM interferon β-1a	60 µg QW	IMPACT[10]	[redacted]	0.67 (0.45, 1.00)
Natalizumab	300 mg Q4W	ASCEND[4]	[redacted]	0.99 (0.65, 1.52)

Again, the ERG acknowledge that the network diagram presented in Figure 5 is sparse, therefore consistency cannot be assumed. The ERG could not assess the assumption of transitivity in detail due to the univariate regression for ARR not presented in the CS. Where data exists, baseline characteristics have been compared (ERG appendix C). We note the historic population sample included in the EU study[8, 9] and the SPECTRIMS study[5, 6] as outlined in Section 4.4.2.1 – however, this is a limitation for both NMA and MAIC comparisons.

4.5.5 Comparing the results from the CS MAIC and the ERG NMA

The ERG note the considerable differences regarding the performance of siponimod compared to the comparator trials between the CS MAIC and the ERG NMA for all outcomes (see Table 37) (the network diagrams and results for 3-month CDP and proportion with 6-months [96w] CDP outcomes are presented in ERG appendix C). For example, difference exists between siponimod versus IM interferon β-1a for 3-month CDP ([redacted] vs. HR 0.81 95% CI: 0.54, 1.22) and siponimod versus SC interferon β-1b for 6-month CDP ([redacted] vs. HR 0.80 95% CI: 0.57, 1.13).

The ERG NMA estimates generally favour siponimod over the comparator treatments, however the results of the NMA are not statistically significant with the exception of siponimod versus SC interferon β-1a 44 µg for the 3-month CDP outcome (HR 0.79 95% CI: 0.66, 0.95) and siponimod versus SC interferon β-1a 22 µg and 44 µg for the ARR outcome ([RR 0.65 95% CI: 0.47, 0.91], [RR 0.65 95% CI: 0.46, 0.92]). The estimates generated from the ERG NMA 6-month CDP and ARR are used in the ERG base-case in the economic appraisal (see Section 6.2).

Table 37. ERG NMA results for all outcomes compared to CS MAIC

				Company MAIC	ERG NMA
3-month CDP	**Comparator**	**Regimen**	**Study ID**	**Siponimod vs. Comparator**	
	SC IFNβ-1a	22 µg TIW	SPECTRIMS	[redacted]	0.90 (0.66, 1.22)
		44 µg TIW	SPECTRIMS	[redacted]	0.79 (0.66, 0.95)
	SC IFNβ-1b	250 µg Q2D	EU Study	[redacted]	1.07 (0.81, 1.41)
	IM IFNβ-1a	60 µg QW	IMPACT	[redacted]	0.81 (0.54, 1.22)
				Siponimod vs. Comparator	
6-month CDP	**Comparator**	**Regimen**	**Study ID**		
	SC IFNβ-1b	250 µg Q2D	NA Study	[redacted]	0.80 (0.57, 1.13)
				Siponimod vs. Comparator	
Proportion with 6-month CDP (96w)[b]	**Comparator**	**Regimen**	**Study ID**		
	Natalizumab	300 mg Q4W	ASCEND	[redacted]	0.73 (0.47, 1.12)
				Siponimod vs. Comparator	
ARR	**Comparator**	**Regimen**	**Study ID**		
	SC IFNβ-1b	250 µg Q2D	NA/Eu Study	[redacted]	0.65 (0.46, 1.04)
	SC IFNβ-1a	22 µg TIW	SPECTRIMS	[redacted]	0.65 (0.47, 0.91)
		44 µg TIW	SPECTRIMS	[redacted]	0.65 (0.46, 0.92)
	Natalizumab	300 mg Q4W	ASCEND	[redacted]	0.99 (0.65, 1.52)
	IM IFNβ-1a	60 µg QW	IMPACT	[redacted]	0.67 (0.45, 1.00)

The ERG acknowledges the exploratory nature of our analyses since we did not conduct a full systematic review to search for potential sources of additional information, and we acknowledge the company's reasoning for ruling out an NMA in section B.2.9. However, the NMA we performed comprises a simultaneous analysis of all potential treatment options and makes full use of the available evidence within a single analysis, as opposed to the MAIC which analysed each comparator trial separately and therefore adds valuable information.

The results of the ERG NMA for 6-month CDP and ARR form the basis of the ERG's base-case model, see Section 6.2 for detailed information of ERG model inputs and assumptions.

4.6 Conclusions of the clinical effectiveness section

4.6.1 The scope and evidence

The company decision problem generally matched the intervention, population, comparator, outcomes, and subgroup(s) as defined in the NICE final scope. The clinical effectiveness section of the CS included six RCT conducted in patients with SPMS (EXPAND, ASCEND, SPECTRIMS, IMPACT, NA, and EU studies).[2, 4-10]

The EXPAND[2] study was a double-blind phase-III placebo-controlled randomised trial that assessed the effectiveness and safety of siponimod. This was the only study included in the CS that provided clinical effectiveness data for siponimod in patients with SPMS. The EXPAND study had no relevant comparator according to the NICE final scope (e.g., interferon β-1b for patients, DMTs used in the UK clinical practice). However, the study is relevant if considered in conjunction with other comparator treatment trials through the MAIC analysis presented in the CS.

The remaining five studies were double-blind placebo-controlled randomised trials of natalizumab (ASCEND),[4] interferon beta-1b (EU study, NA study),[7-9] and interferon beta-1a (SPECTRIMS, IMPACT).[5, 6, 10] The company matched the IPD from the EXPAND study to the aggregate-level data provided in publications of the five trials to indirectly compare the effectiveness of siponimod and other therapies licensed and/or used in the treatment of SPMS across the UK.

The ERG did not identify any potentially relevant ongoing or completed studies not included in SLR of the CS.

4.6.2 The EXPAND study

The EXPAND study[2] enrolled 1,651 patients with SPMS across 31 countries by randomising 1,105 and 546 patients to receive either siponimod (2 mg orally daily) or placebo (taken orally daily), respectively. The study included moderately to severely disabled adults (ages 18-60 years) with active and non-active forms of SPMS with documented EDSS score of 3.0-6.5, history of RRMS, documented EDSS progression in the two years before the study, and no evidence of

relapse in the 3 months before randomisation (see section 4.2 for a fuller description of the EXPAND study).

The ERG consider that overall the EXPAND[2] trial was well conducted, used appropriate statistical methods and had no major protocol violations. However, the ERG note the lack of evidence to confirm the generalisability of the results of EXPAND to the UK population of patients with active forms of SPMS. The number of patients enrolled in EXPAND from the UK was not provided in the CS, CSR or trial publication documentation.

4.6.3 MAIC analysis

In general, the RoB for most domains assessed across the included studies in the MAIC was low, the ERG were generally in agreement with the company's assessment of the RoB.

The results for time to 3-month CDP were not consistent across the comparator treatments. For example, siponimod significantly [redacted] the time to 3-month CDP compared to IM interferon β-1a (60 µg; [redacted]), but not compared to SC interferon β-1a at 22µg ([redacted]), SC interferon β-1a at 44µg ([redacted]), or SC interferon β-1b (250 µg; [redacted]).

Siponimod showed a significant [redacted] in time to 6-month CDP compared to SC interferon β-1b (250 µg; [redacted]).

The ARR was significantly [redacted] with siponimod compared to SC interferon β-1a (22µg/44µg) ([redacted]), but [redacted] compared to interferon β-1a IM 60µg ([redacted]), interferon β-1b SC 250µg ([redacted]), or natalizumab IV 300mg ([redacted]).

The ESS for all comparisons across the matched-adjusted data was reduced substantially compared to pre-matched/adjusted sample size ([redacted]). The ERG considers the ESS included in the economic base-case to be between [redacted].

In the MAIC, the company was unable to match and adjust the compared populations for a number of important study inclusion/exclusion criteria and adjust for *a priori* defined EM. The

relevance of comparator treatments was limited by older studies,[8, 9], and that four of the five trials included predominantly non-relapsing SPMS patients who do not represent the target population in whom siponimod would normally be indicated. The ERG note the evidence would not provide a good representation of the current target patient population. The generalisability is also limited by changes in diagnostic criteria in time, difficulties in accurate diagnosis of SPMS, and variation in diagnostic workups across clinical practices.
A MAIC subgroup analysis in patients with active SPMS was not feasible due to lack of data on patient characteristics, active disease definition, and the outcomes reported for active SPMS subgroups in the publications of comparator treatment trials (SPECTRIMS study, ASCEND study, IMPACT study, EU study, NA study).[4-10] Therefore, the MAIC estimates were based on ITT populations.

In conclusion, the findings from the MAIC analysis should be interpreted with caution, due to unaccounted cross-trial heterogeneity in characteristics of populations, small ESS, limited relevance of the comparator treatment trials' populations, applicability of results to the target populations of patients with active SPMS and lack of independent assessment of the IPD by the ERG.

4.6.4 Remaining uncertainties

Insufficient evidence to compare siponimod with other relevant active treatments:

- In the EXPAND[2] study, siponimod is compared to placebo. There is no active treatment group. There has been no randomised study directly comparing efficacy and safety of siponimod to another relevant comparator in established clinical settings of MS
- The CS included IPD based MAIC analysis which the company suggest would provide more valid estimates between the treatments than NMA. However, the matching and adjustment of the trial groups for certain important factors was not possible. Also, comparator populations in the MAIC were of limited relevance in terms of applicability of results to the target populations with active SPMS
- The ERG were not provided with the MAIC IPD to conduct our independent assessment of the MAIC analysis included in the CS.

Completeness of safety/efficacy data on siponimod:

- Lack of long-term efficacy and safety outcomes for siponimod from EXPAND^2 study are required. The median follow-up period of 21 months in the EXPAND^2 study may have been too short for a more complete assessment of the comparative efficacy-safety profile of siponimod.

Subgroup effects of siponimod:

- In the EXPAND^2 study, the larger beneficial effects of siponimod observed among patients with active disease and with T1 Gd-enhancing lesions at baseline are not definitive and necessitate confirmation from future studies
- FDA approved siponimod for the treatment of relapsing forms of MS including RRMS and active form of SPMS in adults. Non-relapsing (non-active) SPMS however, remained outside the FDA indication. In the EXPAND^2 trial, the effect of siponimod on disability progression (time to 3-month CDP) in patients with non-relapsing (non-active) SPMS was inconclusive (HR=0.87; 95% CI: 0.68, 1.11). There is uncertainty if siponimod is effective in this subgroup of patients. There are no approved treatments for non-relapsing SPMS patients.

Inconsistency of findings in EXPAND study:

- There is uncertainty as to why siponimod did not significantly improve the outcomes based on T25FW test and MSWS-12 scores.

Timely and accurate diagnosis of SPMS:

- There are difficulties in detecting a transitional period from RRMS to SPMS due to overlapping phenotypes of RRMS to SPMS and uncertainties in the diagnosis of SPMS
- Existing imprecise and variable diagnostic criteria across practice are barriers to timely diagnosis of SPMS and reasons for diagnostic misclassification of patients with respect to the forms of MS (RRMS, SPMS, or PPMS).

4.6.5 Conclusion summary

The evidence-base for siponimod is limited in terms of the amount of relevant evidence (one trial EXPAND[2]) and the applicability of the findings of the CS MAIC to relevant populations, comparators, and settings.

The limited evidence indicates some benefits of siponimod in delaying disability progression and reducing relapse rates and disease activity compared to placebo. However, the results of the MAIC should be interpreted with caution, they are not conclusive in determining how siponimod would compare to other established relevant treatments (DMTs) which are available (as outlined in the NICE final scope).

The ERG performed exploratory NMA of 3-month CDP, 6-month CDP, proportion with 6-months (96w) CDP and ARR. We found considerable differences regarding the performance of siponimod compared to the comparator trials between the CS MAIC and the ERG NMA for all outcomes.

The ERG NMA estimates generally favour siponimod over the comparator treatments, however the results of the NMA are not statistically significant with the exception of siponimod versus SC interferon β-1a 44 µg for the 3-month CDP outcome (HR 0.79 95% CI: 0.66, 0.95) and siponimod versus SC interferon β-1a 22 µg and 44 µg for the ARR outcome ([RR 0.65 95% CI: 0.47, 0.91], [RR 0.65 95% CI: 0.46, 0.92]).

The ERG NMA results for 6-month CDP (siponimod vs. SC IFNβ-1b 250 µg Q2D, key input for economic analysis) are considerably different compared the CS MAIC (HR [redacted] vs. HR 0.80 CI: 0.57, 1.13). We discuss the impact of changing the effect estimates (MAIC vs. NMA for 6-month CDP and ARR) on the ICER in Section 6.2. The ERG notes the limitations of our NMA, but we conclude that it is preferable because it comprises a simultaneous analysis of all potential treatment options and makes full use of the available evidence within a single analysis.

5 COST-EFFECTIVENESS

This chapter appraises the economic analysis submitted by Novartis and additional information received from the company in response to the ERG's clarification questions. The ERG critically appraised the evidence submitted (systematic review and economic analysis) and examined the company's electronic model.

The ERG provide a summary of the company's economic analysis, systematic review, cost effectiveness methods and results (base-case, one-way sensitivity, probabilistic sensitivity analysis and scenario analyses) as reported in the submission and/or in the economic model. We compare the company's economic analysis to the NICE reference case,[65] then provide a critique using frameworks on best practices for reporting economic evaluation and economic modelling, to assess the overall reporting quality and validity of these analyses.

The ERG have addressed our concerns by undertaking exploratory analyses where possible.
The submission received by the ERG included:

- A systematic review of the economic evidence for the management of people living with SPMS
- Methods, inputs and assumptions made to undertake the economic analysis, and the company's sensitivity, scenario and subgroup analyses
- Electronic version of the *de novo* Markov model built in Microsoft Excel.

5.1.1.1 Summary of the company's economic analysis

The company undertook a model-based economic analysis to assess the cost-effectiveness of siponimod compared to interferon β-1b for treating people with SPMS. A Markov model was used to depict the natural history of people with SPMS. Information required for the natural history was based on information from the EXPAND trial[2] and the London Ontario database. [11] SPMS disease progression was depicted by means of 10 EDSS levels ranging from EDSS 0 to 9. The hypothetical population entering the model was distributed across EDSS levels 2 to 7, which reflected the EDSS distribution of participants in the EXPAND trial. The mean age of the population was 48 years and 60.1% were female. Other baseline features included years since MS diagnosis (3.76 years) and conversion to SPMS (12.63 years).

Based on the transition probabilities, in each yearly cycle, people could remain in the same SPMS EDSS health state, progress to a more severe EDSS state, regress to a less severe state, or die. On progression to EDSS ≥7, people discontinued DMTs and subsequently followed a natural history progression. In each cycle, people could experience relapses, treatment-related AE or discontinuation of treatment. All of which were captured in separate EDSS health states.

In the model, DMTs delayed the progression of SPMS and reduced the frequency of relapses. Treatment efficacy for siponimod compared to interferon β-1b was based on the company's MAIC (see Section 4.3 for ERG critique). Information about health state utilities for SPMS by EDSS level were based on information from the EXPAND trial[2] and supplemented with health state utility values from Orme et al, (2007)[12] which were derived from utility values from the UK MS survey. Caregivers' utility decrements were based on information obtained from TA127.[66] Utility decrements for people who experienced adverse events by DMT were included in the economic analysis and these were obtained from various sources, mainly previous MS technology appraisals. It was assumed that there is an increased risk of mortality for people with SPMS compared to the general population. Age- and gender-specific all-cause mortality rates for a UK general population were derived from the UK Office for National Statistics (ONS) data,[13] and adjusted using the mortality rates obtained from Pokorski et al. (1997).[14] It was assumed that the increase in mortality for people with RRMS can be applied to people with SPMS.

Information about resource use and unit costs were obtained from various sources, mainly from published literature, British National Formulary,[15] PSSRU,[16] NHS reference costs.[17] Costs related to genotype testing, drug acquisition, administration and monitoring, disease management, treating relapses, and treating adverse events were included in the economic analysis.

The analysis was undertaken from an NHS and PSS perspective. Health outcomes included time in each EDSS state, number of relapses, LYs and QALYs gained over a 50-year time horizon. Costs included disease management costs, drug acquisition, administration and monitoring, costs for treating relapses and costs associated with treating AE. The results were presented as an ICER expressed as cost per QALYs gained. Both costs and effects were discounted at 3.5% per annum. The company undertook a number of sensitivity including PSA, and scenario analysis to determine the robustness of the base-case results to making changes to model inputs and assumptions. Additionally, the company undertook subgroup analysis of people with active SPMS (see Section 4.2.1.7 for description of subgroups).

Base-case results showed that treatment with siponimod compared to interferon β-1b was more costly and expected to yield more QALYs, which resulted in an ICER of approximately [redacted] per QALY. Sensitivity analysis results showed that the HR for 6-month CDP was the most influential model input that had the greatest impact to the ICER. The PSA indicated that at a £30,000 WTP threshold for a QALY, siponimod had a [redacted] (according to the economic model) probability of being cost-effective when compared to interferon β-1b. Results for the active SPMS subgroup analysis showed that siponimod is approximately [redacted] more expensive than interferon β-1b and expected to yield 0.29 and 1.35 more LYs and QALYs, respectively, which equated to approximately [redacted] per QALY.

5.2 ERG comment on company's review of cost-effectiveness evidence

Novartis undertook a SLR to identify cost-effectiveness studies, with the purpose of developing an economic model that could be used to assess the cost-effectiveness of siponimod versus other treatments for people with SPMS. Also the SLR was undertaken to identify studies reporting resource use and costs that could be used in the economic analysis.

5.2.1 Search strategy

Searches for the cost-effectiveness studies SLR and cost and resource use SLR were undertaken together in November 2018, and updated April 2019. An appropriate set of bibliographic databases was searched. The update searches for MEDLINE and Embase were undertaken via different interfaces and there were some differences in the searches. A variety of terms for MS (any type) and economic, cost or resource use were combined in a sensitive search. In addition, a reasonable range of grey literature sources including three trials registers, several HTA websites and relevant conferences (limited to the past four years) were searched or browsed, but no records that had not already been identified by the main bibliographic database searches were found. These are reported with search terms used and number of results retrieved. As new records are not being added to the HTA Database while it moves from the CRD to INAHTA, a targeted web search (using Google or an equivalent search engine) for Health Technology Assessments of siponimod would have been appropriate. The ERG note that the literature searches did not identify the recently published report by ICER[35], but (as noted in the response to clarification question B1) this report was published after the company's update searches were undertaken.

5.2.2 Inclusion criteria

A summary of the inclusion and exclusion criteria used to identify potentially relevant studies is presented in Table 38.

Table 38. Eligibility criteria for cost-effectiveness searches (obtained from CS Appendix G, pages 164-165)

Domain	***Inclusion Criteria***	***Exclusion Criteria***
Population	• *For economic evaluations: adults (aged ≥18 years) with SPMS* • *For studies reporting cost and resource use data: adults (aged ≥18 years) with MS*	• *Adults without SPMS/MS (economic evaluations/cost and resource use studies respectively)* • *MS patients ≤18 years of age* • *Specific cohorts of MS patients (i.e. with any comorbidity)*
Intervention(s)	*Only applicable to economic evaluations:* • *Siponimod* • *Fingolimod* • *Interferon β* • *Ocrelizumab* • *MIS416* • *Glatiramer acetate* • *Natalizumab* • *Masitinib* • *Peginterferon beta* • *Stem cell transplantation* • *Alemtuzumab* • *Dimethyl fumarate* • *Imilecleucel T* • *Idebenone* • *Simvastatin* • *Mitoxantrone* • *Teriflunomide* • *Ibudilast* • *Opicinumab* • *Fluoxetine* • *Rituximab* • *Cladribine* • *Biotin* • *Riluzole* • *Amiloride* *For studies reporting cost and resource use outcomes, any/no intervention was eligible for inclusion*	• *Any other intervention (economic evaluations)* • *NA (cost and resource use studies)*
Comparator(s)	*Only applicable to economic evaluations:* • *Any intervention listed above* • *Placebo* • *Best supportive care* *For studies reporting cost and resource use outcomes, any/no comparator is eligible for inclusion*	• *Any other comparator (economic evaluations)* • *NA (cost and resource use studies)*

Domain	*Inclusion Criteria*	*Exclusion Criteria*
Outcomes	• *Cost-effectiveness of treatment options for SPMS* • *Costs (direct and indirect costs) or resource use associated with MS* o *Impact of any treatment/disease management program on cost/resource use, medical utilisation/treatment pattern only and associated cost, DMT price evaluation studies, and out-of-pocket expenditures only* o *Comparison of cost/resource use by patient specific characteristics including gender, race, and disease severity* • *Comparison of cost or resource use among different disease cohorts including:* o *Treatment types* o *Insurance types* o *Comorbidity* o *Adherence*	*Any other outcomes*
Study design	*Any study reporting relevant outcomes*	*NA*
Country	• *Economic evaluations are not restricted by geography.* • *Studies reporting cost and resource use data conducted in the UK, unless data is reported for SPMS specifically*	*Cost and resource use studies that report on non-UK, non-SPMS populations*
Other considerations	• *Publications with full texts in the English language* • *Conference abstracts published in 2016 or later*	• *Publications without full texts in the English language* • *Conference abstracts published before 2016*

5.2.3 Included studies

The SLR identified 31 records representing 26 individual studies, which comprised five economic evaluations, 10 UK-based MS studies with resource use and costs information, and 11 non-UK SPMS studies with information about resource use and cost for UK. Relevant information from these studies was extracted. Quality appraisal using the Drummond et al,[67] criteria was conducted and summarised in CS Tables 80 and 81, respectively in Appendix G of the CS Document C. Table 39 provides a summary of the key characteristics of these studies.

Table 39. Summary characteristics of the cost-effectiveness studies identified

Author, year and country	Population	Intervention and comparator	Perspective and time horizon	Model type and cycle length	Health states	Evidence synthesis	Source of preference data	Results
Touchette et al., 2003,[68] USA	People with SPMS or RRMS	Mitoxantrone compared to standard care IFNβ-1b compared to standard care IFNβ-1b compare to mitoxantrone	Insurer and societal perspective; 10-year time horizon	Markov model, with annual cycles	Health states based on EDSS score	*Clinical data were sourced from RCTs, for mitoxantrone (MIMS study) and interferon beta 1b (EU SPMS study)*	*Utilities for each EDSS state were obtained from a published study (Parkin et al. NIHR Health Technology Assessment programme, 1998)*	From the insurer perspective (mitoxantrone vs. standard care, approx.US$58,300 per QALY) From the societal perspective (mitoxantrone vs. standard care, Dominates) From the insurer perspective (mitoxantrone vs. standard care, approx. US$741,300 per QALY
Kobelt et al., 2000,[69] Sweden	People with SPMS	IFNβ-1b compared to no treatment	Societal perspective; 10-year time horizon	Markov model, with three-monthly cycles	Health states based on EDSS score	*Clinical data sourced from RCTs (the EU SPMS study)*	HSUV by EDSS were obtained from Henriksson et al, 2000	All costs, SEK 342,700 Indirect costs excluded, SEK 542,000 Informal costs excluded, SEK 435,300 Direct costs only, SEK 634,600
Kobelt et al., 2002,[70] Sweden	People with SPMS	IFNβ-1b compared to no treatment	Societal perspective; 10-year time horizon	Markov model, with three-monthly cycles	Health states based on EDSS score	*Clinical data sourced from RCTs (the EU SPMS study)*	HSUV by EDSS were obtained from	All costs, SEK 257,200 Direct and informal costs, SEK 382,200

Author, year and country	Population	Intervention and comparator	Perspective and time horizon	Model type and cycle length	Health states	Evidence synthesis	Source of preference data	Results
							Henriksson et al, 2000	Direct costs, SEK 447,400 Direct costs only, SEK 634,600
Tappenden et al., 2010,[71], UK	People with SPMS	Autologous HSCT versus mitoxantrone	NHS and PSS perspective; lifetime horizon	Markov model, with annual cycles	Health states based on EDSS score	Clinical data obtained from the EBMT database for HSCT and Lyon registry for mitoxantrone	HSUV by EDSS were obtained from Orme et al., 2007[12]	Effectiveness duration scenario 1 (optimistic-treatment effect sustained indefinitely), Dominated Effectiveness duration scenario 2 (pessimistic-treatment effect sustained for 5 years, then HR is assumed to be 1), £74,200 per QALY Effectiveness duration scenario 3 (middle ground-treatment effect sustained for 10 years, then HR is assumed to be 1), £2,800 per QALY
Forbes et al., 1999,[72] UK	People with SPMS	IFNβ-1b compared to standard care	UK NHS perspective	*Model based on proportion of patients becoming wheelchair*	Not reported	Clinical data obtained from the EU SPMS trial	HSUV by EDSS were obtained from a EuroQoL survey	Base-case results, approximately £1,024,400 per QALY

Author, year and country	Population	Intervention and comparator	Perspective and time horizon	Model type and cycle length	Health states	Evidence synthesis	Source of preference data	Results
				dependent and relapses avoided				

EBMT, European Society for Blood and Marrow Transplantation; EDSS, expanded disability status scale; HR, hazard ratio; HSCT, hematopoietic stem cell transplantation; HSUV, health state utility values; IFN, interferon; NHS, National Health Service; PSS, Personal Social Service; QALY, quality adjusted life-years; RCT, randomised-controlled trial; SEK, Swedish Krona; SPMS, secondary progressive multiple sclerosis

5.2.4 Systematic review of studies reporting resource use and costs

The SLR for resource use and costs associated with treating people with MS was incorporated in the broader cost-effectiveness search; hence a separate search was not undertaken. The ERG consider this to be appropriate.

5.2.5 Systematic review of HRQoL studies

The company undertook a separate search of the literature to identify studies that reported HRQoL values for people with MS and their caregivers, with a specific focus on utility values obtained from a UK population or derived from UK tariffs. Key electronic databases were searched using keywords for evidence published up to January 2019, then updated in April 2019. Other searches included searching manual congress abstracts, HTA websites, grey literature and bibliographies of relevant systematic reviews. Table 40 shows the eligibility criteria used to identify health state utility values, and their caregivers.

Table 40. Eligibility criteria for health related quality of life studies (obtained from Appendix G, pages 277-278)

Domain	***Inclusion Criteria***	***Exclusion Criteria***
Population	• *Adults (aged ≥18 years) with MS* • *Caregivers of adult patients with MS*	• *Adults without MS* • *MS patients <18 years of age*
Intervention(s)	*Any or none*	*NA*
Comparator(s)	*Any or none*	*NA*
Outcomes	• *Utility estimates for health states* • *Mapping algorithms from HRQoL to utilities* • *HRQoL associated with MS and caregiver burden* • *Impact of disease symptoms, medication adherence, employment status, education level on HRQoL*	• *Assessment of cognitive/symptom burden* • *Psychometry study of different PROs*
Study design	*Any study reporting relevant outcomes, unless interventional by nature*	*Interventional studies*

Domain	*Inclusion Criteria*	*Exclusion Criteria*
Other considerations	• *Health state utility values from the UK or using UK tariffs* • *Publications with full texts in the English language* • *Conference abstracts published in 2016 or later*	• *Publications without full texts in the English language* • *Conference abstracts published before 2016*
HRQoL, health-related quality of life; MS, multiple sclerosis; NA, not applicable; PRO, patient-reported outcomes		

Results

The search (original and updated) for literature regarding resource use and costs associated with disease management identified 21 studies from 26 publications, of which 10 were UK-based. For these 10 studies, relevant information about study characteristics as well as baseline characteristics of participants, and results were presented in Tables 101 and 102 pages 557-584 in the CS Appendices.

The SLR identified 57 records representing 56 individual studies that reported health state utility values for people with MS, or using UK tariffs. Key characteristics and results from these studies are presented in Table 97 of the CS Appendices pages 471-548. The company provided baseline characteristics for the participants, sample size, country, methods (questionnaires) used to elicit values and the tariffs used to value health states, and the overall results. Results were either presented as an overall mean utility (with standard deviation), by each EDSS or categorised (mild, moderate or severe) by severity of MS. Though a formal critique of the studies was not presented, the company provided information about consistency with the reference standard, as well as relevance to the decision problem.

5.2.6 Conclusions

The company's systematic review of the cost-effectiveness evidence comparing interventions for treating people with SPMS identified those studies undertaken in a UK setting. The ERG are satisfied that the search criterion is unlikely to have missed any UK-based economic studies. However, there is potential for other studies to have been missed because it appears that a targeted Google search was not undertaken. The search for economic evaluations also included studies reporting resource use and costs for treating MS. The ERG are satisfied with the company's search and that all UK-based studies had been identified. The ERG are satisfied with

the company's search to identify studies reporting HRQoL. However, the ERG would welcome further critique/appraisal of the identified studies.

5.2.7 Additional literature searching undertaken by the ERG

The ERG undertook targeted searches and searches of the grey literature to identify studies that estimated the cost-effectiveness of DMTs for the treatment of people with SPMS. Searches involved; a) updating the company's cost-effectiveness and cost/resource use searches of Medline (Ovid) and Embase (Ovid) from April 2019 to October 2019, b) a targeted search of websites using the Google search engine for Siponimod and HTA, and c) targeted searches of Medline (Ovid) and Embase (Ovid) for MS, HRQoL, United Kingdom and EQ-5D. The targeted searches identified a report conducted by the Institute for Clinical and Economic Review (ICER), 2019.[35] An overview of summary characteristics are provided in Table 41

5.2.7.1 Summary of the ICER 2019 report

A model-based economic analysis was conducted to assess the cost-effectiveness of siponimod compared to best supportive care (BSC) for treating people with SPMS, and a subgroup with active SPMS (people with evidence of relapses within two years of enrolment). A Markov model was used to depict the natural history of people with SPMS. Information required on BSC was based on information from the BSC arm of the EXPAND trial.[2] SPMS disease progression was depicted by means of 9 EDSS levels ranging from EDSS 1 to 9 and dead. The hypothetical population that entered the model was distributed across EDSS levels 2 to 7, which reflected the EDSS distribution of the participants in the EXPAND trial.[2] The mean age of the population was 48 (SD = 4.8) years, with 61% females. Other baseline features included years since MS diagnosis (3.76 years) and conversion to SPMS (12.63 years).

Based on the transition probabilities, in each yearly cycle people could remain in the same SPMS EDSS health state, progress to a more severe EDSS state, or die. Transitions did not allow for an improvement in disability. In each cycle, people may also experience relapses, all of which were captured in separate EDSS health states. It should be noted that a no stopping rule was applied to the base-case population, but applied to the active SPMS population in the subgroup analysis. The stopping rule was set at progressing to EDSS ≥7; where people immediately follow the progression for a natural history cohort, which was derived from the London Ontario dataset.[11]

DMTs delayed the progression of SPMS and reduced the frequency of relapses. Treatment efficacy (relative risk of 3-month CDP and relapses) for siponimod compared to placebo was based on the EXPAND trial.[2] Information about health state utilities for SPMS by EDSS level were based on data obtained from Hawton et al. (2016)[73] and from Orme et al,[12] in scenario analysis. Caregivers utility decrements were based on information obtained from Acaster et al, (2013).[74] Utility decrements for people who experienced adverse events were excluded from the analysis, as the AE recorded in the EXPAND trial.[2] were considered to be mild and similar to best supportive care (see Section 4.2.7 for discussion of AE). It was assumed that there is an increased risk mortality for people with SPMS compared to the general population. Age- and gender-specific all-cause mortality rates for a US general population were obtained from the US life tables using the Human Mortality database's US-specific tables and adjusted using the mortality rates obtained from Pokorski et al., (1997).[14]

The economic model included the costs associated with genotype testing, drug acquisition, administration and monitoring, disease management, productivity costs and costs for treating relapses.

The base-case analysis was undertaken from a societal perspective. Health outcomes included LY, ambulatory LYs and QALYs gained over a life-time horizon. Cost outcomes included drug costs and other direct costs. The results were presented as ICERs expressed as cost per LYG, cost per ambulatory LYG and cost per QALYs gained. Both costs and effects were discounted at 3% per annum. The company undertook a number of sensitivity including PSA, and scenario analyses. Additionally, the company undertook subgroup analysis of people with active SPMS. Also, undertook an analysis that compared interferon β-1b versus siponiomod, with treatment efficacy results derived from the company's MAIC.

Base-case results showed that treatment with siponimod compared to BSC was more costly and yielded more QALYs, which resulted in an ICER of approximately US$1.15 million per QALY. Sensitivity analysis results showed that the model was very sensitive to the HR for CDP, thus having the greatest impact to the ICER. The probabilistic sensitivity analysis results indicated that siponimod compared to BSC is unlikely to be cost-effective at accepted WTP threshold for the cost per additional QALY.

Alternative scenario analyses were undertaken that compared siponimod to other DMTs. In the absence of studies that directly compared siponimod to these DMTs, the clinical effective evidence was based on the MAIC analysis submitted by the company, which was reported as academic-in-confidence. ICER 2019 stated that from these DMTs, the trial that included interferon β-1b to placebo included participants that were similar to the licence indication for people treated with beta interferons and siponimod. This analysis used the MAIC results for CDP3M, derived from matching patient-level data from the EXPAND trial with aggregate data from the EU study.[8, 9] Briefly, the MAIC adjusted for differences in age, EDSS, and the proportion of participants relapse-free in two years prior to the study. Using these results, siponimod was more costly and effective than interferon β-1b, which resulted in an ICER of approximately US$2.11 million per QALY gained.

Table 41. Summary characteristics of the cost-effectiveness studies identified by the ERG

Author, year and country	Population	Intervention and comparator	Perspective and time horizon	Model type and cycle length	Health states	Evidence synthesis	Source of preference data	Results
Institute for clinical and economic review (ICER), 2019[35]	Adults ≥18 years with secondary progressive multiple sclerosis, and a subgroup of people with active SPMS	Siponimod compared to best supportive care	Health system perspective (direct medical costs)	Markov model with annual cycle lengths	Health states based on expanded disability status scale score, which ranged from EDSS 1 to 9 and dead	Base-case analysis uses information from the EXPAND clinical trial, and in scenario analysis siponimod was compared to a DMT which has been studied in SPMS patients based on the results of a matching-adjusted indirect comparison	Health state utility values were obtained from Hawton et al., 2016[73] and in scenario analysis based on those obtained from Orme et al., 2007.[12] Caregiver's disutility were obtained from Acaster et al., 2013[74]	Base-case results showed that siponimod compared to best supportive care had an incremental cost-effectiveness ratio of US$1,150,000 per QALY in the overall population. Probabilistic results showed that at a threshold of $US150, 000 there was a zero probability that siponimod was cost-effective in either the overall population or the active secondary progressive multiple sclerosis population. Scenario analysis results showed that siponimod compared to best supportive care had an incremental cost-effectiveness ratio of US$433,000 per QALY in the active secondary progressive multiple sclerosis population. Using treatment effects derived from the matching-adjusted indirect comparison siponimod compared to interferon β-1b had an incremental cost-effective ratio of US$2,110,000 per QALY
DMT, disease modifying therapy; EDSS, expanded disability status scale; QALY, quality adjusted life-years; SPMS, secondary progressive multiple sclerosis								

5.3 Summary and critique of company's submitted economic evaluation by the ERG

In this section, we report an appraisal of the company's economic analysis against the NICE reference case for technology assessment.[65] We provide a summary of the company's illustrative model structure, as well as the clinical (treatment effect on CDP, ARR, treatment discontinuation and mortality) and economic evidence (DMT acquisition costs, health state costs for SPMS, treatment of relapses and AE) used to parameterised the economic model. We provide a critique of the methods and inputs used in the economic analysis.

5.3.1 NICE reference case checklist

The ERG have undertaken an evaluation of the CS in relation to the NICE reference case.[65] Findings are summarised in Table 42.

Table 42. NICE reference case checklist

Attribute	Reference case and TA Methods guidance[65]	Does the *de novo* economic evaluation match the reference case
Defining the decision problem	The scope developed by NICE	Decision problem clearly stated and is in line with the scope developed by NICE
Comparator(s)	Therapies routinely used in the NHS, including technologies regarded as current best practice for this population	Comparator included in the base-case was interferon β-1b. Scenario analyses included other DMTs used outside of their marketing authorisations
Patient group	As per NICE final scope, the population refers to: People living with RRMS	As per NICE final scope
Perspective costs	NHS & Personal Social Services	Yes
Perspective benefits	All health effects on individuals	Yes
Form of economic evaluation	Cost-effectiveness analysis	Cost-effectiveness analysis
Time horizon	Sufficient to capture differences in costs and outcomes between the technologies being compared	Lifetime time horizon
Synthesis of evidence on outcomes	Systematic review	Systematic review was undertaken by the company
Outcome measure	QALY	Results reported in terms of quality adjusted life-years
Health states for QALY	Described using a standardised and validated instrument	Yes
Benefit valuation	Time-trade off or standard gamble	The standard UK EQ-5D tariff is used, which is based upon time-trade off

Attribute	Reference case and TA Methods guidance[65]	Does the *de novo* economic evaluation match the reference case
Source of preference data for valuation of changes in HRQoL	Representative sample of the public	Yes
Discount rate	An annual rate of 3.5% on both costs and health effects	Yes
Equity	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes
Probabilistic modelling	Probabilistic modelling	The company undertook PSA and reported these results
Sensitivity analysis		The company undertook sensitivity and several scenario analyses
EQ-5D, EuroQol five dimensions; HRQoL; health-related quality of life; IFN, interferon; NHS; National Health Service; NICE; National Institute for Health and Care Excellence; PSA; probabilistic sensitivity analysis; QALY, quality-adjusted life years		

5.3.2 Model structure

The company used a cohort-based Markov model to depict the natural history of people with SPMS (Figure 6). The model illustrates disability progression and regression (reduction to disability) between EDSS levels, and the relapses people with SPMS may experience. People with SPMS occupied one health-state at any given time, which ranged from EDSS 0 to 9 in increments of 1.

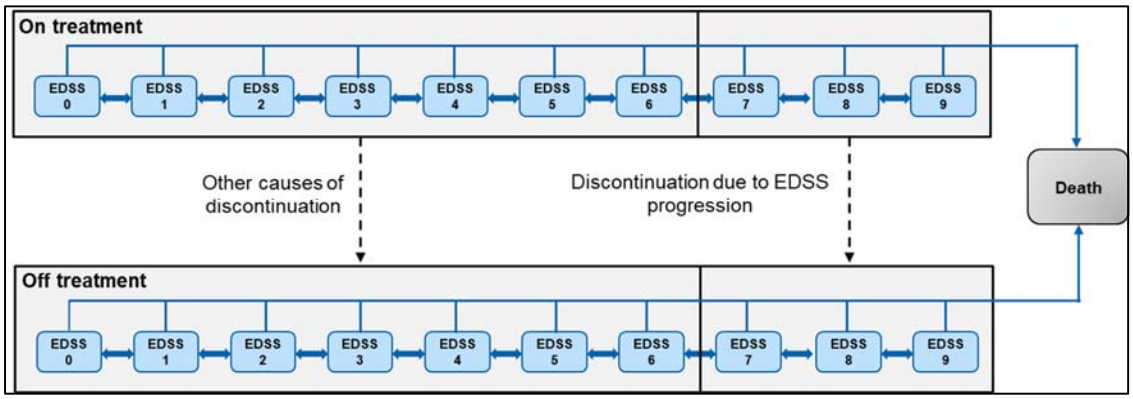


Figure 6. Illustrative model structure (obtained from the CS Document B Figure 14)

The model began with a hypothetical cohort of people with SPMS receiving DMT (siponimod or interferon β-1b, distributed across EDSS levels <6 (see Table 43). Though not explicitly stated in the CS, it was assumed that the cohort all had either the CYP2C9*2*3 or *1*3 genotype (see Section 2.2.1 for description of genotype testing). The starting age of the population entering the

model was 48 years, with 60.1% females. Transitions between health states were bi-directional, where people could remain in the same health state, or regress (improve) or progress. People who discontinued treatment either due to progressing to EDSS level ≥7 or experiencing AE, discontinued DMTs and received BSC, where progression and relapses followed the natural history (based on the EXPAND trial[2] and the London Ontario dataset[11] of the disease. From each EDSS health state there was a risk of mortality. People incurred costs and accrued benefits (QALYs) in each model cycle, depending on the EDSS health state occupied.

ERG summary

The Markov model appears to capture the key important features of people living with SPMS. However, based on the illustrative model structure, people with SPMS could regress to less severe health states (i.e. improve), which is not consistent with the ICER 2019 report,[35] where progression between SPMS health states was unidirectional.

5.3.3 Population

The population included in the economic analysis is similar to the population included in the EXPAND trial,[2] participants have a mean age of 48 years, a mean time since MS diagnosis of [redacted] years, and a mean time to conversion to SPMS of [redacted] years. The starting distribution (reported in Table 43) of people in each EDSS level was based on the placebo group of the EXPAND trial,[2] with majority of the cohort in EDSS 6 (55.33%) and EDSS 4 ([redacted]).

Table 43. Characteristics of people included in the model (obtained from CS, Document B)

Characteristic	***Obtained from CS, Document B***		**ICER report[35] [a]**
	ITT population	***Active SPMS***	**ITT population**
Mean age (in years)	*48*	[redacted]	48 (4.8) years
% male patients	*39.9%*	[redacted]	39%
Baseline EDSS distribution in percentages (assuming cohort size of 1,000 patients)			
EDSS 0	*0%*	*0.00%*	0.0%
EDSS 1	*0%*	*0.00%*	0.0%
EDSS 2	[redacted]	[redacted]	0.5%
EDSS 3	[redacted]	[redacted]	14.0%
EDSS 4	[redacted]	[redacted]	14.0%
EDSS 5	*16.09%*	[redacted]	16.1%
EDSS 6	*55.33%*	[redacted]	55.3%
EDSS 7	[redacted]	[redacted]	0.2%
EDSS 8	*0%*	*0.00%*	0%
EDSS 9	*0%*	*0.00%*	0%
Total	***100%***	***100%***	**100%**

EDSS, expanded disability status scale; ITT, intention-to-treat, SPMS, secondary progressive multiple sclerosis
a- *'Estimated based on categorical percentages' (ICER report page 45)*[35]

The ERG noted that there were some differences between the starting populations/distributions in the CS document compared to the ICER 2019 report,[35] even though there were derived from the EXPAND trial.[2] The ERG were unable to understand or explain why these differences exist.

5.3.4 Intervention and comparators

The base-case compared siponimod versus interferon β-1b, and in scenario analyses comparisons were made against other DMTs (dimethyl fumarate, fingolimod, glatiramer acetate, interferon β-1a (Avonex®), interferon β-1a (Rebif® 22µg and 44µg), natalizumab, ocrelizumab and teriflunomide) used outside their marketing authorisation. Table 44 presents the DMTs and their posology included in the cost-effectiveness analysis.

Table 44. Intervention and comparators included in the cost-effectiveness analysis

Disease-modifying therapy	Dosing schedule
Intervention	
Siponimod	2mg daily
Comparators	
Interferon β-1b	250µg every other day
IM interferon β-1a 30	30µg once weekly
Interferon β-1a 22	22µg three times per week
Interferon β-1a 44	44µg three times per week
Glatiramer acetate 20mg/40mg	20mg or 40mg once daily
Teriflunomide	14mg once daily
Dimethyl fumarate	240mg twice daily
Ocrelizumab	600mg every six months

IM, intramuscular

The DMTs included in the economic analysis were in line with the NICE final scope (see Section 3.3 for ERG comparison). The ERG agree that it was appropriate to exclude cladribine and alemtuzumab in the economic analysis. However, it would have been beneficial to see a comparison between siponimod and BSC, and a comparison between interferon β-1b and BSC. This comparison would provide a face validity assessment as to whether the model is predicting the same treatment effect as the MAIC or the EXPAND trial.[2] Scenario analysis results which contain DMTs used outside their MA should be treated with caution. The ERG consider that

separate MAICs would need to be undertaken, as the clinical evidence is not available from one study. We also note that performing separate MAICs would alter the population included in the analysis.

5.3.5 Perspective, time horizon and discounting

The analysis was conducted from the NHS and PSS perspective, which is in line with the NICE Guide to the Methods of Technology Appraisal.[65] The model assumed a lifetime horizon of 50 years, which was long enough to capture the long-term costs and benefits of DMTs. In the base-case, the 3.5% per annum discount rate was applied to the costs incurred and benefits accrued. Several sensitivity and scenario analyses were undertaken by the company. Scenario analysis results were reported for an analysis from a societal perspective and based on changes made to the time horizon.

5.3.6 Transitions

To demonstrate the movement of people between the EDSS health states in the model, information was required for transitions between the SPMS health states (and from treatment to no treatment) and death. In the absence of DMTs, transition probabilities for the natural history cohort were based on data from the EXPAND[2] placebo group and supplemented with transition probabilities derived from the London Ontario dataset.[11] A multi-state modelling approach was used to derive the transition probabilities from the placebo group (N=546) in the EXPAND trial.[2] Table 45 shows the natural history transitions between the EDSS health states. As displayed in Table 45, people can remain, progress to more severe EDSS states, or regress to less severe health states.

ERG summary

Where data permitted, the natural history transitions were derived from data from the placebo group of the EXPAND trial and supplemented with data from London Ontario dataset. Using this approach resulted in people being able to regress to less severe EDSS levels, which may be more common in RRMS as opposed to SPMS. In discussion with the ERG clinical advisor, we understand that over the long-term, people with SPMS will progress (or rarely plateau); but in the short-term, if people have a relapse from which they recover they could improve before they

worsen again. The ERG have made the assumption that the short timeframe is approximately 2-3 months. However, the transitions in the model are yearly, thus making regressions very rare.

Two natural history databases were briefly discussed in the CS, the London Ontario[11] and the British Columbia databases. Previous MS appraisals have used the London Ontario and British Columbia databases alone or in addition to trial data to reflect the natural history of people with SPMS and, to our knowledge there are no other natural history databases.

The ERG considers the London Ontario database to be more appropriate. The London Ontario dataset enforced an analytic rule that there could be no regression (or reductions in disability), so disability scores for people can only worsen over time.[11] Second, transitions based on the EXPAND trial data were collected over a 2-year time horizon, whilst data from the London Ontario study were collected over 25 years. Table 46 shows the London Ontario SPMS-SPMS transition matrix obtained from the economic model. The ERG note that the matrix derived from the London Ontario dataset[11] alone is not consistent with other SPMS-SPMS matrices used in the ICER 2019 report, see Table 47.[35] The ERG consider that the transition probabilities are different from previous appraisals, which raises concerns about the transition probabilities used to supplement those derived from the EXPAND trial.[2]

Table 45. Natural history transition probability matrix based on information from the EXPAND2 placebo group and London Ontario database11 (base-case)

EDSS From/to		EDSS state (to)										
		0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
EDSS state (from)	**0**	1.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
	1	0.000	1.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
	2	0.000	0.000	0.455	0.375	0.099	0.041	0.027	0.002	0.000	0.000	0.000
	3	[redacted]								0.002	0.000	0.000
	4									0.006	0.000	0.000
	5									0.023	0.000	0.000
	6									0.048	0.000	0.000
	7	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.644	0.349	0.006	0.000
	8	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.991	0.008	0.000
	9	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	1.000	0.000
	10	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	1.000

EDSS, expanded disability status scale

Table 46. Natural history transition probability matrix based on information from the London Ontario database11 (obtained from NH-Disability Progression worksheet)

EDSS From/to		EDSS state (to)										
		0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
EDSS state (from)	**0**	1.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
	1	0.0000	1.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
	2	0.0000	0.0000	0.4550	0.3750	0.0991	0.0412	0.0270	0.0020	0.0007	0.0000	0.0000
	3	0.0000	0.0000	0.0000	0.5630	0.2803	0.0885	0.0610	0.0053	0.0019	0.0000	0.0000
	4	0.0000	0.0000	0.0000	0.0000	0.4821	0.2808	0.2178	0.0131	0.0061	0.0000	0.0000
	5	0.0000	0.0000	0.0000	0.0000	0.0000	0.3396	0.5966	0.0408	0.0228	0.0002	0.0000
	6	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.8701	0.0810	0.0484	0.0005	0.0000
	7	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.6446	0.3490	0.0064	0.0000
	8	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.9916	0.0084	0.0000
	9	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	1.0000	0.0000
	10	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	1.0000

EDSS, expanded disability status scale

Table 47. Natural history transition probability matrix based on information from the London Ontario database (obtained from ICER 2019)

EDSS From/to		EDSS state (to)										
		0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
EDSS state (from)	**0**	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
	1	0.0000	0.7692	0.1538	0.0769	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
	2	0.0000	0.0000	0.6357	0.2713	0.0620	0.0233	0.0078	0.0000	0.0000	0.0000	0.0000
	3	0.0000	0.0000	0.0000	0.6291	0.2527	0.0769	0.0330	0.0027	0.0055	0.0000	0.0000
	4	0.0000	0.0000	0.0000	0.0000	0.4854	0.3504	0.1387	0.0073	0.0182	0.0000	0.0000
	5	0.0000	0.0000	0.0000	0.0000	0.0000	0.6325	0.3173	0.0221	0.0261	0.0020	0.0000
	6	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.7631	0.1903	0.0446	0.0020	0.0000
	7	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.8046	0.1891	0.0062	0.0000
	8	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.9258	0.0742	0.0000
	9	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	1.0000	0.0000
	10	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	1.0000

EDSS, expanded disability status scale

5.3.6.2 Annualised relapse rates (ARR)

The economic model required information about relapses experienced over time and during each cycle. ARR were derived from information obtained from the placebo group of the EXPAND trial,[2] the UK MS Survey[12] and Patzold and Pocklington (1982)[75], which are presented in Table 48. The UK MS Survey collected information on the total number of people who experienced a relapse by EDSS and the number of years since diagnosis. Whereas, Patzold and Pocklington (1982) undertook a regression analysis to investigate the relationship between ARRs and the number of years since diagnosis.[75] The natural history ARR were applied to people who discontinued DMT, and a relative risk based on the MAIC was applied to the natural history ARR to estimate the frequency of relapses experienced in each EDSS level by DMT. Further details of these relative risks are reported in Table 49

Table 48. Natural history ARR

EDSS	EXPAND,[2] Patzold and Pocklington (1982)[75] and UK MS Survey[12]		Patzold and Pocklington (1982)[75] and UK MS Survey[12]
	ITT	Active SPMS	ITT
0	0.000	0.000	0.000
1	0.000	0.000	0.000
2	0.465	0.465	0.465
3	[redacted]	[redacted]	0.875
4	[redacted]	[redacted]	0.545
5	[redacted]	[redacted]	0.524
6	[redacted]	[redacted]	0.453
7	[redacted]	[redacted]	0.340
8	[redacted]	[redacted]	0.340
9	[redacted]	[redacted]	0.340

ARR, annualised relapse rates; EDSS, expanded disability status scale; SPMS, secondary progressive multiple sclerosis

5.3.6.3 Treatment discontinuation

The model allowed for treatment discontinuation due to people experiencing AE, lack of effectiveness, and to progression to EDSS ≥7. This is in line with the clinical guidelines from the Association of British Neurologists (ABN) which recommend that treatment should be discontinued when people progress to a non-ambulatory state.[37] People who discontinued DMTs received BSC. Discontinuation rates were based on time-to-event information obtained from the treatment group in the EXPAND trial[2](see Section 4.2.7 for further description). Fully-fitted parametric curves were used to show the rate at which people discontinued treatment during the

trial and beyond the trial duration. The choice of parametric fit was based on visual inspection and assessing the AIC. According to these criteria, the exponential and Weibull distributions were considered the most appropriate, with the company choosing the Weibull distribution, as the exponential showed a high number of people remaining on treatment beyond the trial duration (Document B page 105). Figure 7 presents the Weibull distribution fitted to the discontinuation data for siponimod and interferon β-1b. Discontinuation rates for interferon β-1b and other comparators presented in the CS were obtained by applying the relative risk derived from the Bucher ITC to the discontinuation rate of siponimod.

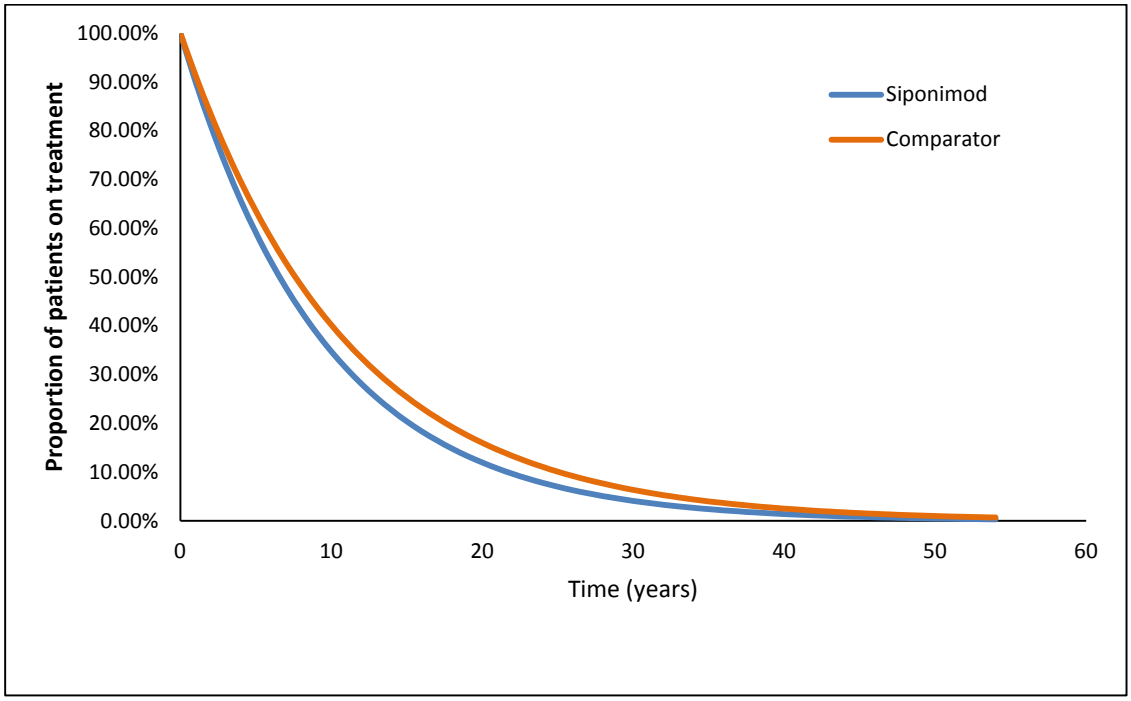


Figure 7. Weibull distribution fitted to all-cause discontinuation data

ERG summary

On inspection of the parametric curves presented in CS Document B page 105, CS Figure 15 reflects the exponential distribution fitted to the all-cause discontinuation data and Figure 7 reflects the Weibull distribution used in the company's base-case. Assessment of the curves suggest that people receiving siponimod discontinued treatment at a higher rate than people receiving interferon β-1b. It should be noted that these discontinuation rates are based on fitting parametric curves to 3-year trial data, then extrapolating over a 50-year time horizon. This may not reflect benefits or treatment discontinuation in a real-world setting. The ERG consider the use

of discontinuation rates observed from a real-world setting may be more appropriate, if they are available.

It was unclear to the ERG if the discontinuation rates presented in the CS were applied to the time spent in the model or time spent in the EDSS health state, which can potentially lead to over or underestimating treatment discontinuation. It addition, it was not clear if the parametric curves were fitted individually or simultaneously.

5.3.7 Mortality

The model required mortality rates to show the rate at which people died within in each cycle over the modelled time horizon. People with MS are at increased risk of death compared to the all-cause mortality for the general population. Mortality was accounted for in the model by using age- and gender-specific all-cause mortality risks, weighted by the proportion of males and females in the model, and adjusted with different relative risks. Age- and gender-specific mortality from the general population were obtained from the ONS (2016),[13] with all–cause mortality risk adjusted by disease-specific risks obtained from Pokorski et al., (1997).[14]

Table 49 presents the relative risks applied to all-cause mortality for the UK general population. As EDSS severity increases, the relative risk associated with mortality increases. It was assumed that people with SPMS have the same increased risk of mortality as people with other forms of MS (RRMS and PPMS).

Table 49. Relative risks for SPMS mortality (interpolated)

EDSS	Relative risks derived from Pokorski et al., (1997)[14]
0	1.0000
1	1.4316
2	1.6002
3	1.6372
4	1.6740
5	1.8420
6	2.2726
7	3.0972
8	4.4472
9	6.4540
EDSS, Expanded disability status scale; SPMS, secondary progressive multiple sclerosis	

ERG summary

The age- and gender- specific all-cause mortalities have been adjusted appropriately to capture the increase mortality in people with SPMS. These have been applied appropriately in the model.

5.3.8 Stopping rules

People in the model discontinued DMT upon progressing to EDSS ≥7, which is in-line with ABN guidelines. After treatment was discontinued, people immediately commenced best supportive care for the remainder of the model time horizon or until they die.

5.3.9 Treatment effects

Treatment effectiveness is captured in the model by applying relative risks to the natural history transition probabilities to derive separately the transition matrix for people receiving treatment with siponimod and interferon β-1b (Extavia®) for confirmed disability progression and frequency of relapses. These hazard ratios for 6-month CDP were based on the results from the North American study, which compared siponimod versus placebo (HR= 0.92, 95% CI: 0.71, 1.20), and the MAIC analysis for siponimod versus placebo ([redacted]). To our knowledge the model does not directly use the 6-month CDP HR derived from the MAIC ([redacted]) for the comparison between siponimod and interferon β-1b (Extavia®). This was applied as a probability to forward transitions, and it was assumed that the relative risk remain constant for the duration of the model, once on treatment. Likewise, for ARR, the results were obtained from the North American study for the comparison of interferon-β-1b (Extavia®) (RR = 0.65, 95% CI: 0.48, 0.88), and the MAIC analysis for siponimod versus placebo ([redacted])

DMTs are considered to have a direct impact on CDP and relapse frequency. However, there will be an indirect benefit to mortality. DMTs delay progression, therefore avoids the time to progressing to more severe health states, which carry a higher risk of mortality compared to the less severe health states.

5.3.9.1 Confirmed disability progression (CDP)

This section summarises how the treatment effect had been applied in the economic model. A full description regarding how the treatment effect was derived and its critique can be found in Section 4.3. The treatment effects in the form of HR were applied to the forward transition probabilities of the natural history cohort to determine disease progression for each treatment-specific DMT. It was assumed that DMTs have no direct impact on the backward transition probabilities (i.e. no direct impact to people who regress to less severe EDSS states). Treatment benefit stopped as soon as people discontinued treatment, then disability progression and relapses were based on the natural history cohort. It is assumed that there is no residual benefit from taking DMTs and that people who have not been treated with a DMT progress at the same rate as the natural history cohort.

5.3.9.2 Relapse

DMTs have a direct impact on the frequency of relapses people experience. The effect of DMTs on relapse rates required information from a placebo or natural history cohort, and the treatment effect of each DMT compared to placebo in the form of a relative risk. The base-case model used ARR derived from the placebo group of the EXPAND trial[2]and Patzold and Pocklington (1982).[75] In the scenario analyses the ARR were derived using information from the UK MS Survey[12] and Patzold and Pocklington (1982).[75]

As presented in Table 50, there are some differences between the ARR derived from the EXPAND trial[2] when compared to those obtained from the UK MS Survey.[12] Differences include; lower relapse frequencies reported across the majority of the EDSS levels when using EXPAND trial data and people with EDSS ≥7 appear to have more frequent relapses compared to people with EDSS <7.

Table 50. ARR for a natural history cohort, using EXPAND trial,2 Patzold and Pocklington (1982)75 and values from UK MS Survey12 and Patzold and Pocklington (1982)75

EDSS	ARR, using EXPAND[2] and Patzold and Pocklington (1982)[75]	ARR, using UK MS Survey[12] and Patzold and Pocklington (1982)[75]
	SPMS	SPMS
0	0.000	0.000
1	0.000	0.000
2	0.465	0.465
3	[redacted]	0.875
4	[redacted]	0.545
5	[redacted]	0.524
6	[redacted]	0.453
7	[redacted]	0.340
8	[redacted]	0.340
9	[redacted]	0.340

ARR, annualised relapse rates; EDSS, expanded disability status scale; MS, multiple sclerosis; SPMS, secondary progressive multiple sclerosis

The model included the proportion of relapses which required hospitalisation [redacted] and relapses that did not [redacted]. This information was derived from the EXPAND trial data.[2] It was assumed that there was no difference between the intervention and comparator in the effectiveness of DMTs on relapse severity. Table 51 provides the treatment effectiveness estimates based on the six individual trials identified in the CS SLR[2, 4-10](see Section 4.3.1) and the MAIC analyses (see Section 4.4 for ERG critique). The effect of each DMT was applied to the ARR estimated from the natural history information.

Table 51. Relative risks for annualised relapse rates for each DMT compared to placebo

Comparator	***Comparator DMT vs placebo RR (95% CI)***	***Siponimod vs placebo RR (95% CI)***	***Source***
Interferon β-1b (Extavia®)	*0.65 (0.48–0.88)*	[redacted]	*MAIC - EXPAND[2] & NA Study & EU Study[7-9]*
Interferon β-1a (Rebif® 22 µg)	*0.69 (0.56–0.84)*	[redacted]	*MAIC - EXPAND[2] & SPECTRIMS[5, 6]*
Interferon β-1a (Rebif® 44 µg)	*0.69 (0.56–0.85)*	[redacted]	*MAIC - EXPAND[2] & SPECTRIMS[5, 6]*
Natalizumab (Tysabri®)	*0.45 (0.32–0.63)*	[redacted]	*MAIC - EXPAND[2] & ASCEND[4]*
Interferon β-1a (Avonex®)	*0.67 (0.49–0.90)*	[redacted]	*MAIC - EXPAND[2] & IMPACT[10]*
Siponimod	*-*	*0.45 (0.34; 0.59)*	*EXPAND[2]*
CI, confidence interval; DMT, disease modifying therapy; MAIC, matching-adjusted indirect comparison; RR, relative risk;			

Table 52 presents the results for the effect of DMTs on ARR for the comparison between siponimod versus interferon β-1b. These results suggest that, over the model time horizon, treatment with siponimod is expected to yield 3.17 relapses (not requiring hospitalisation) per annum per person compared to 3.30 for people undergoing treatment with interferon β-1b. Treatment with siponimod is expected to yield 0.07 fewer relapses requiring hospitalisation compared to interferon β-1b.

Table 52. Model output for the expected yield of relapses per year per person over the model time horizon

DMTs	**Relapse not requiring hospitalisation**	**Relapse requiring hospitalisation**
Interferon β-1b	0.41	0.22
BSC	2.89	1.51
Total	3.30	1.72
Siponimod	0.45	0.23
BSC	2.72	1.42
Total	3.17	1.65
BSC, best supportive care; DMT, disease modifying therapy		

A detailed critique of the MAIC and its results are presented in Section 4.4. The treatment efficacy for CDP and ARR derived from the MAIC were applied to an ITT population as used in the model; thus indicating that the efficacy results are generalisable, which may be a strong assumption given the evidence available (see Section 4.5 for ERG critique and ERG additional analysis). Each cycle of the model requires information about the patient disposition to calculate costs and utilities across each EDSS state for the model time horizon, and the company

submission left us unclear on the logical steps required for the mechanics of the model. Applying the treatment effect illogically may potentially bias the benefit associated with treatment.

5.3.10 Health-related quality of life

Utility calculations for people with SPMS in the model required information on their health state, and on disutilities associated with AE from DMTs, relapses experienced, and on caregivers' disutilities. The base-case uses health state utility values were obtained from the EXPAND trial,[2]and supplemented with health state values from Orme et al, (2007).[12] These values are presented in Table 53.

Table 53. Summary of utility values used in company's economic

EDSS	*Utility values EXPAND[2] and Orme et al., (2007)[12]*	*Orme et al., (2007)[12] (used in scenario analysis)*
0	*0.825*	*0.825*
1	*0.754*	*0.754*
2	*0.660*	*0.660*
3	[redacted]	*0.529*
4	[redacted]	*0.565*
5	[redacted]	*0.473*
6	[redacted]	*0.413*
7	[redacted]	*0.252*
8	*-0.094*	*-0.094*
9	*-0.240*	*-0.240*
EDSS, expanded disability status scale		

HRQoL information was collected using the EQ-5D-3L questionnaire in the EXPAND trial,[2] which is in line with the NICE reference case.[65] However, as stated in the CS (Document B Page 108), there were few people in the EXPAND trial with EDSS states 0,1,2,8 and 9. Additionally, there was considerable uncertainty in the EQ-5D information collected from people with EDSS 2 to 8. Given these limitations, the ERG considers that the utility values derived from the trial data may not be generalisable to people with SPMS who are in these EDSS levels. Alternative health state utility values obtained from Orme et al, (2007)[12] were used in scenario analysis. For EDSS levels 3 to 7, the values derived from the EXPAND trial[2] data are higher than those from the Orme study.[12] Using the values from the EXPAND trial for these health states (EDSS 3 to 7) places a greater benefit (accrual of more QALYs) for people who occupy these health states in the economic model compared to Orme et al.[12]

The model captures disutilities associated with relapses and AE as well as disutility associated with providing care for people with MS. The relapse disutility of [redacted] was derived from EXPAND trial data.[2] Due to the low number of relapses in the trial, disutilities according to severity were not derived. Alternative relapse disutility values obtained from the literature are provided.[12, 76]

The model also captures the quality of life impact on people who have experienced AE. The ERG describe the AE reported in the EXPAND trial in Section 4.2.7. Treatment-specific disutilities associated with AE are presented in Table 54. These average annual AE were derived from taking the proportion of AE from the EXPAND trial for serious ([redacted]) and non-serious ([redacted]) events.

Table 54. Average annual adverse event disutility by DMT

Disease modifying therapy	Average disutility
Siponimod	[redacted]
Dimethyl fumarate	[redacted]
Fingolimod	[redacted]
Glatiramer acetate	[redacted]
Interferon β-1a (Avonex®)	[redacted]
Interferon β-1a (Rebif® 22 µg)	[redacted]
Interferon β-1a (Rebif® 44 µg)	[redacted]
Interferon β-1b (Extavia®)	[redacted]
Natalizumab	[redacted]
Ocrelizumab	[redacted]
Teriflunomide	[redacted]
BSC	0.0000

Caregiver's disutilities used in the base-case were obtained from Gani et al.,(2008)[77] which were also used in TA127[66] Alternative values from Acaster et al., (2013)[74] were used in scenario analyses. Table 55 displays the higher disutility experienced by caring for people with EDSS 5 and 6, as opposed to the more severe EDSS health states from the Acaster et al (2013) values.[74] The ERG consider it more appropriate to use the disutilities obtained from TA127[66] as these are more in line with our expectation that disutilities increase as the EDSS severity increases. The differences relate to the availability of long term and respite care for those in more severe health states.

Table 55. Caregivers' utility decrements by EDSS

EDSS	Obtained from TA127[66]	Obtained from Acaster et al, 2013[74]
0	0.000	0.000
1	-0.001	-0.002
2	-0.003	-0.045
3	-0.009	-0.045
4	-0.009	-0.142
5	-0.020	-0.160
6	-0.027	-0.173
7	-0.053	-0.030
8	-0.107	-0.095
9	-0.140	-0.095

EDSS, expanded disability status scale; SPMS, secondary progressive multiple sclerosis; TA, technology appraisal

ERG summary

The company's economic analysis captured HRQoL of people living with SPMS, by including EDSS health state utilities, disutilities associated with AE from DMTs, relapses experienced, and also caregivers' disutilities. The company used utility values derived from the EXPAND trial[2], data were supplemented with values from Orme et al., (2007)[12] where utility values were not available for specific health states. Given the paucity of participants in some EDSS states, the results from the EXPAND trial may not be generalisable to a wider population in these health states. Therefore, the ERG considers the Orme[12] utility values more appropriate in the base-case. The ERG are in agreement with the disutilities used in the company base-case. From the model output, it is unlikely that the results of the expected QALYs yielded to be biased.

5.3.11 Resource use and costs

In the base-case the cost assessment was based on assigning resource use and costs for siponimod and interferon β-1b, disease management costs, relapse costs, and treatment of AE costs from the NHS and PSS perspective.

5.3.11.1 Intervention and comparators

Table 56 presents the annual drug acquisition costs, drug administration and monitoring costs, and treatment of AE for each DMT. Annual drug acquisition costs are based on the list price for each DMT, where available PAS prices are presented. Additionally, DMT administration and monitoring, and adverse event management costs are presented for year 1 and subsequent years.

Table 56. Annual drug acquisition, administration and monitoring and AE management costs by DMT

Disease modifying therapy	Drug acquisition costs		Drug administration and monitoring costs		AE management costs	
	Year 1	Year 2+	Year 1	Year 2+	Year 1	Year 2+
Siponimod	[redacted]	[redacted]	£733	£307	£22.19	£22.19
Patient access scheme price	[redacted]	[redacted]				
Dimethyl fumarate	£17,910	£17,910	£641	£230	£47.56	£47.56
Fingolimod	£19,176	£19,176	£1,157	£288	£62.35	£62.35
Patient access scheme price	[redacted]	[redacted]				
Glatriamer acetate	£6,704	£6,704	£527	£283	£63.96	£63.96
Interferon β-1a (Avonex®)	£8,531	£8,531	£546	£292	£87.60	£87.60
Interferon β-1a (Rebif® 22 µg)	£8,003	£8,003	£548	£292	£85.60	£85.60
Interferon β-1a (Rebif® 44 µg)	£10,608	£10,608	£548	£292	£85.60	£85.60
Interferon β-1a (Extavia®)	£7,264	£7,264	£546	£292	£102.90	£102.90
Patient access scheme price	[redacted]	[redacted]				
Natalizumab	£14,740	£14,740	£7,575	£7,787	£387.64	£387.64
Ocrelizumab	£19,160	£19,160	£2,288	£1,742	£143.12	£143.12
Teriflunomide	£13,538	£13,538	£378	£228	£6.72	£6.72
Best supportive care	£0	£0	£0	£0	£0.00	£0.00

5.3.11.2 Health state management costs

The company assumed that disease management costs for people with RRMS are applicable to people with SPMS. EDSS-specific management costs were based on costs obtained from TA527[78] and inflated to current values using the hospital and community health service (HCHS) pay and price index from PSSRU 2018 (Curtis and Burns., 2018).[16] The underlying resource use were based on the UK MS cross-sectional postal survey, with a sample size of 2,048 participants (16% response rate from people in the UK MS database).[12] Resource use information from TA320[18] was re-analysed, then inflated to 2014/15 prices. Table 57 presents the disease management costs included in the model. The company stated that no scenario analyses were undertaken around these costs because at the NICE appraisal committee meeting for TA527[78] these values were considered to be the most appropriate as they are based on the best available data.

Table 57. Disease management costs by EDSS level (2017/18 values)

EDSS	SPMS health state management costs (£)	SPMS health state costs obtained from TA320[18] and uprated to current prices (2017/18)
0	£965	£1,301
1	£1,004	£1,340
2	£736	£1,071
3	£4,024	£4,360
4	£1,949	£2,285
5	£3,307	£3,644
6	£4,415	£4,750
7	£11,621	£11,955
8	£28,304	£28,637
9	£22,648	£22,982

EDSS, expanded disability status scale; SPMS, secondary progressive multiple sclerosis

The ERG conducted a search of the NICE website for recent (within the last two years) NICE technology appraisals of DMTs used to treat MS. We identified alternative SPMS specific health state management costs. In Table 57 we present disease management costs obtained from a recent NICE technology appraisal. There are some differences between the disease management costs from TA320[18] and those used in the company's base-case. Using the lower disease management costs may result in an underestimate of the mean total costs.

5.3.11.3 Relapse costs

Depending on the EDSS health state, people within the model may experience relapses which require hospitalisation or not. CS Document B pages 115-117, Table 71 and Table 72 state that the base-case used relapse management costs were obtained from TA527.[78] It was assumed that relapse management costs were the same regardless of disease severity, and that the costs are applicable to people with SPMS. Table 58 shows the costs used in the base-case and alternative relapse management costs, all in 2017/18 prices.

Table 58. Relapse management costs by severity

Source	Relapse not requiring hospitalisation	Relapse requiring hospitalisation
Base-case		
TA527[78] – RSS model and ScHARR analysis	£4,357	£4,357
Scenario analysis		
Hawton et al, 2016[73]	£407	£3,825
Tyas et al, 2007[79]	£1,962	£1,962
RSS, risk sharing scheme; ScHARR, School of Health and Related Research; TA, technology appraisal		

The company base-case uses uprated relapse management costs obtained from TA527.[78] The costs obtained from the RSS were uprated from 2001 price. This assumes that the management and resource use for treating relapses have not changed since 2001, which may be a strong assumption. In cross-checking against the economic model, the 'Settings' worksheet indicated that the source of relapse costs in the base-case was Tyas et al., 2007[79], therefore using the £1,962 value, which corresponded to the base-case ICER of [redacted] reported by in the CS.

Cost of treating adverse events

Resource use and costs associated with the treatment of serious and non-serious AE were included in the analysis. Cost of treating AE were based on the annualised incidence of each adverse event, the proportion of adverse events, the resource use and unit cost for treating each adverse event. Table 56 presents the annual AE management costs by DMT.

The ERG accepts the methodology and the assumptions made to derive the annual AE management costs.

5.3.12 Overview of model assumptions and ERG critique

In Table 59, we present the company's modelling assumptions with comments from the ERG. This set of model assumptions is taken from CS Document B, Section B.3.6.2.

Table 59. Model assumptions with ERG's comments

Parameter	Base-case assumption	Justification	ERG's comment
Patient population	*The patient population in EXPAND and the Active SPMS subgroup are representative of the NHS population eligible for treatment with siponimod*		The ERG agrees with these assumptions.
Relapse severity	*Treatment does not have any impact on severity or duration of relapses*		This is a plausible assumption
Transition probabilities	*Patients with SPMS may progress or regress in EDSS states and treatment effect is applied to EDSS progression but not regression:*		Recent technology appraisals have included a natural history transition matrix, which does not allow for a regression in disability. We agree with the company that treatment effect should only be applied to EDSS progression.
Treatment discontinuation	*Patients discontinue treatment once they reach EDSS score 7.0*	*In line with ABN guidelines, patients with SPMS who reach EDSS 7.0 discontinue treatment, as the EXPAND trial does not provide any evidence to determine efficacy in patients with EDSS ≥7.0*	As stated, this is in line with the ABN guidelines
Treatment effect	*Treatment benefits are accrued only during the treatment period*	*It is assumed that treatment effects of DMTs are accrued only during DMT treatment; after discontinuing the DMT, patients will move to BSC and no residual treatment effect is modelled in patients*	Plausible assumption
Treatment effect: mortality	*Treatment has no direct survival benefit:*	*It is assumed that DMTs will not have any impact on mortality rate*	This is a plausible assumption

Parameter	Base-case assumption	Justification	ERG's comment
		directly. However, patients receiving siponimod might survive for a longer period vs patients receiving BSC as siponimod slows disability progression (patients in lower EDSS states have lower mortality risk compared with patients in higher EDSS states)	
Relapses	*Relapses have no residual effect on EDSS*	*Impact of relapses are included as costs and disutility according to relapse severity. It is assumed that relapse will not have any impact on EDSS progression or regression*	CS document B pg. 109 stated that disutilities according to relapse severity were not derived due to the low number of relapses reported in the trial. Assuming that relapses have no impact on EDSS progression or regression appears to be feasible.
Adverse events	*Constant rate of AEs*	*AEs are assumed to occur at a constant rate in patients receiving DMTs and are assumed to stop after discontinuing DMTs. A similar approach was used in previous NICE RRMS submissions.*	Assumptions all feasible.

ABN, Association of British Neurologists; AE, adverse events; DMT, disease modifying therapy; EDSS, expanded disability status scale; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis;

5.3.13 Cost-effectiveness results

The following section presents the company's cost-effectiveness results reported in CS Document B. The company's base-case results are reported based on the PAS in the form of a discount on the cost of siponimod and interferon β-1b. Table 60 reports the disaggregated results for treatment with siponimod and interferon β-1b in terms of relapses, time spent in health states, LY and QALYs, which were reported in the economic model.

5.3.13.1 Company's base-case results

The results in Table 60 demonstrate that over the model time horizon, siponimod was approximately [redacted] more costly than interferon β-1b and yielded 0.30 and 1.32 more LY and QALYs, respectively, which equated to an ICER of approximately [redacted] per QALY gained.

Table 60. Company's base-case deterministic results

Treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Interferon β-1b	[redacted]	15.86	3.17	-	-	-	-
Siponimod	[redacted]	16.16	4.49	[redacted]	0.30	1.32	[redacted]
ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALYs, quality adjusted life-years							

5.3.13.2 Company's probabilistic sensitivity analysis results

Probabilistic sensitivity analysis was undertaken based on the outcome costs per QALY only. In PSA, each parameter is assigned a distribution to reflect the pattern of its variation and the ICER results are calculated based on randomly selecting variables from each distribution. The company stated that distributions were assigned to all model input parameters. The mean estimates for the PSA results are presented in Table 61. The ERG note that the PSA results are in-line with the deterministic results.

Table 61. Company's probabilistic sensitivity analysis results

Treatment	Costs	QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Interferon β-1b (Extavia®)	[redacted]	3.12	-	-	-
Siponimod	[redacted]	4.41	[redacted]	1.25	[redacted]
ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALYs, quality adjusted life-years					

One thousand simulations of the incremental costs and QALYs for siponimod compared to interferon β-1b were plotted on a cost-effectiveness plane, along with their cost-effectiveness acceptability curves. The scatterplot (see Figure 8) shows that there is some variation in the

incremental costs and incremental effectiveness (QALYs). The ERG note that some of the simulations are in the north-west quadrant, indicating that siponimod is more costly but less effective than interferon β-1b. Additionally, some of the simulations are in the south-east quadrant indicating that siponimod dominated interferon β-1b. However, the majority of the simulations are in the north-east quadrant, which suggests siponimod is more costly but more effective than interferon β-1b.

Figure 8. Scatterplot of strategies on the cost-effectiveness plane, company base-case using PAS prices

Figure 9 presents the results in the form of a cost-effectiveness acceptability curve (CEAC) for the comparison between siponimod and interferon β-1b. The curves show the proportion of the simulations in which treatments are deemed to be cost-effective at different WTP thresholds, which ranged from £0 to £100,000 per QALY. At a WTP threshold of £20,000 per QALY siponimod compared to interferon β-1b had a [redacted] probability of being cost-effective and, at a WTP threshold of £30,000 per QALY the probability increased to [redacted]

Figure 9. Cost-effectiveness acceptability curve, company base-case using PAS prices

The ERG considers the distributions used around key model input parameters, and the assumption of 20% of the mean for the standard error (SE) in the absence of confidence intervals to be appropriate. However the ERG has several concerns relating to the PSA:

1. The ERG is unclear if the PSA is using the SEs of 20% of the mean for the ARR treatment effect for siponimod and interferon β-1b or the confidence intervals derived from the MAIC. Using the former could potential lead to under or over-estimating the uncertainty around the ARR treatment effect in the PSA.

2. The ERG would have welcomed a feature in the model to allow or select other distributions to test the impact of changes on the results of using other plausible distributions.

3. The ERG noted a typographical error or inconsistency between the probability of siponimod being cost-effective at a £30,000 per QALY WTP threshold. CS Document B page 122 indicated a [redacted] probability but the economic model states [redacted].

4. The ERG note that the model does not include any uncertainty around the number of people with CYP2C9 metaboliser status.

5.3.13.3 Company's deterministic sensitivity analysis results

Several deterministic one-way sensitivity analyses were undertaken to determine the key drivers of the economic model for the comparison between siponimod versus interferon β-1b. Parameters were varied according to their upper and lower bound of their respective 95% confidence intervals or by assuming bounds of ±20% of the input value. Results were reported in the form of tornado diagrams. Figure 10 is the ICER tornado diagram, which presents the key drivers of the model and their impact to the deterministic base-case results.

Figure 10. ICER tornado diagram for the comparison between siponimod and interferon β-1b, using the PAS

The results in Figure 10 show the 10-most influential model inputs to the base-case ICER, with the HR for 6-month CDP (siponimod and interferon β-1b) having the greatest impact. The ERG note that using the upper estimate of the HR for 6-month CDP (making siponimod less effective) resulted in an ICER of approximately [redacted] per QALY and using the lower estimate (making

siponimod more effective) resulted in an ICER of approximately [redacted] per QALY. Using the lower estimate of the HR for 6-month CDP for interferon β-1b when compared to siponimod gave an increase to the base-case ICER of approximately [redacted] per QALY. Conversely, using the upper estimate of the HR for 6-month CDP for interferon β-1b reduced the base-case ICER to approximately [redacted] per QALY.

In summary, the company included a comprehensive list of model input parameters in their sensitivity analysis to show which inputs were the key drivers of the economic analysis. The ERG consider this analysis to be appropriately conducted.

5.3.13.4 Company's scenario analysis results

The company undertook several scenario analyses (based on the comparison of siponimod versus interferon β-1b, and siponimod compared the other DMTs) to assess the impact of each change to the base-case deterministic results. The following scenarios presented in Table 62 were undertaken for the siponimod and interferon β-1b comparison only.

Table 62. Description of the company's scenario analyses in comparison to the base-case

Scenario	Base-case analysis	Scenario analysis
Natural history disability progression		
1	Combining EXPAND[2] placebo-arm data with London Ontario data[11]	London Ontario database
Natural history disability progression		
2	Combining EXPAND[2] placebo-arm data with London Ontario data	British Columbia
Natural history of relapses		
3	Combining EXPAND[2] data with Patzold and Pocklington (1982)[75] plus UK MS survey[12]	Patzold and Pocklington (1982)[75] plus UK MS survey[12]
Treatment discontinuation		
4	Time-dependent	Time-independent
Adverse events		
5	EXPAND[2] data supplemented with TA533	EXPAND with individual comparator
Health state utility values		
6	EXPAND[2] data plus Orme et al.,(2007)[12]	Orme et al.(2007)[12]
Relapse disutility		
7	EXPAND[2] data	Orme et al, (2007).[12]
Relapse disutility		
8	EXPAND[2] data	Ruutiainen et al.,(2016)[76]

Caregiver disutility		
9	TA127[66]	Acaster et al., (2013)[74]
Relapse costs		
10	Tyas et al, (2007)[79]	TA527[78]
Relapse costs		
11	Tyas et al, (2007)[79]	Hawton et al., (2016)[73]
MS, multiple sclerosis; TA, technology appraisal		

The results for each change made and the impact to the base-case results are presented in Table 63 for the comparison between siponimod and interferon β-1b. Using transition probabilities derived from the British Columbia database to reflect disability progression in a natural history cohort of people living with SPMS, had the greatest impact to the base-case ICER. This scenario, resulted in an increase to the incremental costs and a decrease to the incremental QALYs, with an ICER of approximately [redacted] per QALY.

Table 63. Results of the base-case scenario analysis for the comparison between siponimod and interferon β-1b

Scenario	Interferon β-1b		Siponimod		Incremental		ICER
	Total costs	**Total QALYs**	**Total costs**	**Total QALYs**	**Incremental costs**	**Incremental QALYs**	
Base-case	[redacted]	3.17	[redacted]	4.49	[redacted]	1.32	[redacted]
Natural history disability progression (London Ontario)	[redacted]	2.08	[redacted]	3.20	[redacted]	1.12	[redacted]
Natural history disability progression (British Columbia)	[redacted]	5.64	[redacted]	6.73	[redacted]	1.08	[redacted]
Natural history of relapses	[redacted]	3.15	[redacted]	4.47	[redacted]	1.32	[redacted]
Treatment discontinuation	[redacted]	3.18	[redacted]	4.88	[redacted]	1.70	[redacted]
Adverse events	[redacted]	3.22	[redacted]	4.49	[redacted]	1.27	[redacted]
Health state utility values	[redacted]	2.08	[redacted]	3.25	[redacted]	1.17	[redacted]
Relapse disutility	[redacted]	3.17	[redacted]	4.50	[redacted]	1.32	[redacted]
Relapse disutility	[redacted]	3.17	[redacted]	4.50	[redacted]	1.32	[redacted]
Caregiver disutility	[redacted]	2.25	[redacted]	3.37	[redacted]	1.12	[redacted]
Relapse costs	[redacted]	3.17	[redacted]	4.49	[redacted]	1.32	[redacted]
Relapse costs	[redacted]	3.17	[redacted]	4.49	[redacted]	1.32	[redacted]
ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life-years							

The results accurately reflect the changes made in each scenario analysis. However, the ERG notes that no scenario analysis was undertaken on treatment costs. Using alternative values might

have resulted in a change to the base-case ICER. Additionally, other scenario analyses were undertaken that were not reported in CS Document B, for example, using CDP3M as the primary endpoint and excluding treatment discontinuation.

Scenario analyses: using alternative comparators

In addition to interferon β-1b1, other comparators (interferon β-1a 22µg and 44µg, glatiramer acetate, and natalizumab) were included in the economic analysis in the form of scenario analyses (Table 64). See Table 65 for the assumptions made by the company for these scenario analyses, along with the ERG critique.

Table 64. Scenario analyses results

Scenario	Comparator		Siponimod		Incremental		ICER
	Total costs	Total QALYs	Total costs	Total QALYs	Incremental costs	Incremental QALYs	
Avonex Rebif 22 Rebif 44	*See base-case vs Extavia as a conservative proxy for this analysis*						
Glatiramer acetate	£273,117	3.17	[redacted]	4.49	[redacted]	1.32	[redacted]
Natalizumab	£347,414	2.79	[redacted]	3.54	[redacted]	0.75	[redacted]
Dimethyl fumarate	317,805	2.99	[redacted]	3.71	[redacted]	0.72	[redacted]
Fingolimod	[redacted]	2.98	[redacted]	3.71	[redacted]	0.73	[redacted]
Ocrelizumab	£328,853	2.95	[redacted]	3.71	[redacted]	0.76	[redacted]
Teriflunomide	£300,734	3.71	[redacted]	3.01	[redacted]	0.71	[redacted]

ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life-years

Table 65. Scenario analysis assumptions using alternative comparators

Company's assumption	ERG's critique
TA527 concluded that interferons were equal in efficacy and that Extavia was the least costly; TA527 applied one set of efficacy inputs to all interferons and glatiramer acetate and the approach taken is aligned to that	To our knowledge, equal efficacy for the interferons and glatiramer acetate are based on the pooled RSS treatment estimates for people with RRMS. The assessment group undertook an analysis using the pooled RSS estimates.
Therefore, in the absence of 6-month CDP data for these comparators, the base case ICER vs Extavia using 6-month CDP is, by definition, higher than any ICER vs other more costly interferons (Extavia reported the lowest ICER in TA527 when considering the same efficacy for all treatments); consequently, no new ICERs are presented for these scenarios	The ERG are in agreement with the company that there is only treatment efficacy information for interferon β-1b for people with SPMS. In TA527, [78] the assessment group undertook an economic analysis, which assumed equal efficacy using the pooled RSS estimates.
TA527 concluded that interferons were equal in efficacy and applied one set of efficacy inputs to all interferons and glatiramer acetate and the approach taken is aligned to that	It should be noted that the TA527[78] conclusion is based on people in the RSS. The underlying assumption here is that equal efficacy would be seen in people living with SPMS.
As the cost of glatiramer acetate is not known to be greater than that for Extavia (in contrast to the other interferons noted above), an analysis was undertaken where the price of Extavia was replaced by the list price of glatiramer acetate (Brabio)	The ERG considers this to be a strong assumption.
Natalizumab uses the proportion of patients with 6-month CDP at week 96 MAIC OR and ARR from the ASCEND trial	The ERG considers this to be appropriate. In the trial publication for natalizumab (ASCEND[4], time to 6-month CDP data were not available. The company, therefore used the proportion of patients with 6-month CDP at 96 weeks (the relative effectiveness for this outcome was assumed to be interchangeable with relative effectiveness on the time to 6-month CDP at 96 weeks). This assumption enabled the company to include the natalizumab trial in the economic model. The ERG consider this to be appropriate given the lack of information available.
Comparators use 6-month CDP HR and ARR equal to 1 – this is a reasonable assumption for CDP, given the lack of RCT evidence and that even DMTs with high efficacy in RRMS have failed to demonstrate efficacy on CDP in SPMS, but is biased against the comparator for ARR where ongoing efficacy is likely; however, it is known that relapse efficacy has very little influence on the ICER	This appears to be a reasonable assumption as the results of the assessment group's NMA showed that there was no statistical significant difference between the DMTs in comparison to placebo for disability progression confirmed at 3-months in people with SPMS. More information is provided in Section 4.5
Siponimod uses EXPAND ITT 6-month CDP HR and ARR	This appears to be a plausible assumption.

ARR, annualised relapse rate; CDP, confirmed disability progression; DMT, disease modifying therapy; HR, hazard ration; ICER, incremental cost-effectiveness ratio; ITT, intention-to-treat; MAIC, matching-adjusted indirect comparison; RRMS, relapsing-remitting multiple sclerosis; TA, technology appraisal

Subgroup analysis results

The company undertook a subgroup analysis for people with active SPMS for the comparison between siponimod and interferon β-1b only. Due to the paucity of trials undertaken within this population, the company assumed that the transition probabilities for disease progression and the treatment efficacy derived from the MAIC (see Section 4.3.4). This was used in the base-case, and the company assumed that this can be applied to this subgroup, which can be considered a conservative assumption. Key differences between the base-case and the subgroup analysis are the baseline characteristics and the starting distribution. Subgroup analysis results showed that siponimod is expected to cost approximately [redacted] more than interferon β-1b and is expected to yield 1.35 more QALYs (Table 66).

Table 66. Scenario analysis results: active SPMS subgroup analysis

Treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Extavia®	[redacted]	16.23	3.11	-	-	-	-
Siponimod	[redacted]	16.52	4.46	[redacted]	0.29	1.35	[redacted]

ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALYs, quality adjusted life-years; SPMS, secondary progressive multiple sclerosis

5.3.14 Model validation and face validity check

Model validity comprised clinical and health economic expert opinion and input in the development of the model structure and assumptions. In addition, the company sought guidance from previous NICE technology appraisals in RRMS and PPMS undertaken between 1999 and 2019. No model cross validation of the outputs was undertaken due to the lack of UK-based economic models comparing siponimod with other DMTs for treating people living with SPMS. Instead, the company compared their model structure and inputs against previous MS technology appraisals. The company stated that their sensitivity analysis showed similar findings regarding which inputs had the greatest impact to the base-case ICER. Several tests on the model were undertaken for face validity.

The ERG considers the steps taken for model validation and face validity to be appropriate. However, with respect to model validation, the ERG is aware of a report published in 2019 (ICER 2019)[35] which provides the clinical and cost-effectiveness results for the comparison between siponimod and best supportive care. It also included scenario analysis results comparing

siponimod versus interferon β-1b. The ERG note that this was not a UK-based model, however the report contains valuable information that can be used to compare the economic models[35]

5.4 Exploratory and sensitivity analyses undertaken by the ERG

5.4.1 The ERG's suggested amendments

Based on our critique of the company's economic model, the ERG made changes to the company's model to explore the impact of each change to the company's base-case results. The suggested changes, along with the ERG's justification are presented below:

- Source of disability progression and relapse effectiveness from the ERG's NMA

This exploratory analysis draws on the results of the ERG's NMA for the indirect comparison between siponimod compared to interferon β-1b (detail is provided in Section 4.5). The company's base-case uses results from their MAIC for the clinical outcomes CDP and ARR. MAIC analyses aims to provide comparative evidence where a direct comparison in not available and other evidence synthesis techniques are not appropriate.[35] The company's MAIC matched IPD from the EXPAND trial[2] with aggregate data from the NA Study[7] according to balanced study populations, then adjusted for potential effect modifiers.[35] Full details of our critique of the company's MAIC are presented in Section 4.4. Briefly, the ERG consider that the findings from the MAIC analysis should be interpreted with caution, due to unaccounted cross-trial heterogeneity in characteristics of populations, small ESS, limited relevance of the comparator treatment trials' populations, applicability of results to the target populations of patients with active SPMS and lack of independent assessment of the IPD by the ERG. Given our concerns and uncertainties associated with the company's MAIC, we considered that our NMA analysis may be more appropriate and robust.

- Natural history transition probabilities based on the London Ontario dataset[11] derived by the company

The transition matrix in Table 67 shows that only forward transitions are allowed; hence, there is a zero probability for people having an improvement in disability. As a result of using this transition matrix the company's illustrative model structure is invalidated. Figure 11 shows that only forward transitions are allowed in this exploratory analysis.

Table 67. Natural history matrix based on information from the London Ontario database11 (obtained from NH-Disability Progression worksheet)

EDSS From/to		EDSS state (to)										
		0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
EDSS state (from)	**0**	1.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
	1	0.000	1.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
	2	0.000	0.000	0.455	0.375	0.099	0.041	0.027	0.002	0.000	0.000	0.000
	3	0.000	0.000	0.000	0.563	0.280	0.088	0.061	0.005	0.001	0.000	0.000
	4	0.000	0.000	0.000	0.000	0.482	0.280	0.217	0.013	0.006	0.000	0.000
	5	0.000	0.000	0.000	0.000	0.000	0.339	0.596	0.040	0.022	0.000	0.000
	6	0.000	0.000	0.000	0.000	0.000	0.000	0.870	0.081	0.048	0.000	0.000
	7	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.644	0.349	0.006	0.000
	8	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.991	0.008	0.000
	9	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	1.000	0.000
	1	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	1.000

EDSS, expanded disability status scale

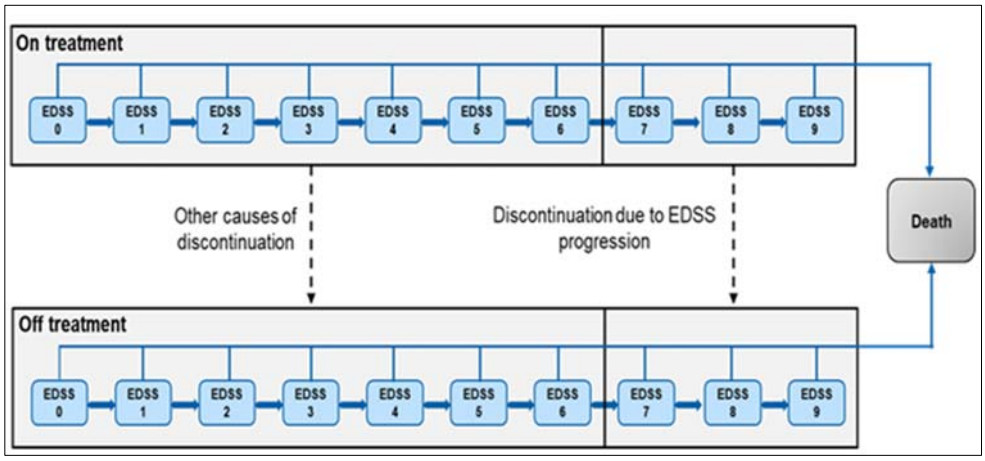


Figure 11. ERG's amendment to the company's illustrative model mode structure

- Exponential distribution fitted to discontinuation data

A series of parametric models were fitted to the all-cause discontinuation EXPAND[2] trial data. The Weibull model was chosen based on the combination of the AIC and the clinical plausibility of the estimated proportion of people who remained on treatment. However, the ERG considers that the exponential curve had the lowest AIC and also plausible estimates. Figure 12 shows the

fully fitted exponential curves to the all-cause discontinuation data for siponimod and interferon β-1b. Table 68 shows the proportion of people remaining on treatment by parametric distribution.

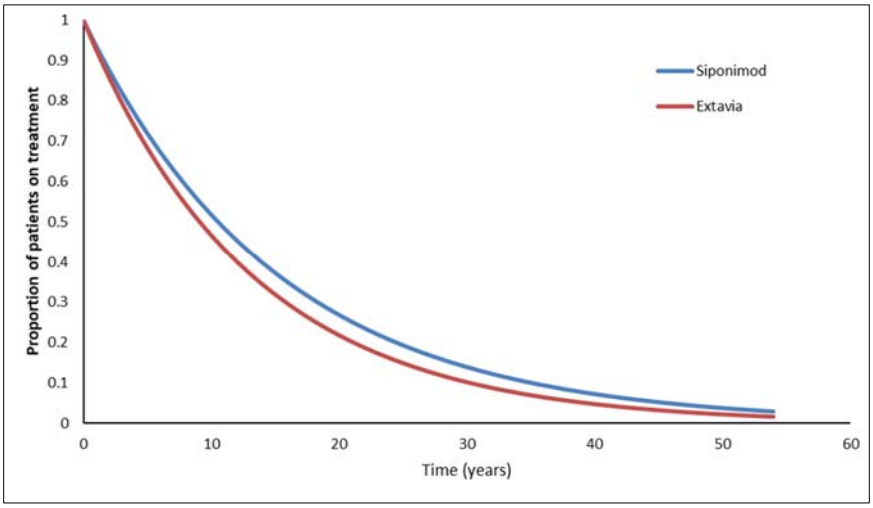


Figure 12. Exponential distribution fitted to discontinuation data

Table 68. Proportion of people remaining on treatment by parametric distribution

Overall survival	Exponential	Weibull (base-case)	Log-normal	Log-logistic	Gompertz
Siponimod					
1-year	90.08%	90.12%	89.30%	89.96%	89.91%
3-year	73.09%	73.01%	75.24%	73.58%	73.51%
5-year	59.30%	59.10%	66.33%	61.80%	60.98%
10-year	35.17%	34.75%	52.70%	43.63%	40.42%
25-year	7.33%	7.00%	34.47%	22.60%	17.08%
50-year	0.54%	0.48%	22.56%	12.26%	8.47%
Interferon β-1b					
1-year	91.38%	91.41%	90.70%	91.28%	91.23%
3-year	76.30%	76.23%	78.22%	76.74%	76.68%
5-year	63.70%	63.52%	70.14%	66.00%	65.25%
10-year	40.58%	40.17%	57.47%	48.84%	45.73%
25-year	10.49%	10.09%	39.76%	27.62%	21.69%
50-year	1.10%	1.00%	27.52%	16.24%	11.81%

- Treatment effect for siponimod compared to interferon β-1b (Extavia®) applied as a rate as opposed to a probability

The company's base-case applied the treatment effectiveness as a probability to the forward transitions of the natural history transition matrix. However, the ERG considers it more appropriate to apply the effectiveness as a rate because the HR assumes that at any given point the

ratio of the hazards (interferon β-1b (Extavia®) versus siponimod) is the same for 6-month CDP and ARR. Applying the treatment effectiveness as a probability is concerned that the event occurs but not the timing of the event, and this may not be consistent with this type of model.

- Health state utility values obtained from Orme et al., 2007[12]

The HSUVs derived from Orme[12] data may be more generalisable than those from the EXPAND [2] trial, due to the larger number of participants in each EDSS health state (Table 69).

Table 69. Health state utility values obtained from Orme et al., 200712

Expanded disability status scale	***Orme et al. 2007[12]* *(used in scenario analysis)***
0	*0.825*
1	*0.754*
2	*0.660*
3	*0.529*
4	*0.565*
5	*0.473*
6	*0.413*
7	*0.252*
8	*-0.094*
9	*-0.240*

- Using the cost of £4,357 for treating relapses obtained from TA527[78] – RSS model and ScHARR analysis

Table 71 page 115 of the CS Document B states that the base-case model included a cost of £4,357 for treating relapses, but the economic model uses the relapse treatment cost of £1,962, which is based on an uprated cost from Tyas et al, (2007).[79]

- Costs of £35 for genotyping borne by the company

In response to the ERG's clarification question (B3), the company stated that all costs associated with genotype testing will be borne by the company.

- Health state management costs obtained from TA320[18]

The base-case assumed that disease management costs are the same as for people living with RRMS. However, we are aware of SPMS specific disease management costs from TA320. [18]

SPMS management costs from TA320 are based on a regression analysis of the UK MS Survey resource use information, with updated costs applied to derive an estimate of unit costs associated with each EDSS health state (Table 70).

Table 70. Disease management costs by EDSS state obtained from TA32018 and inflated to 2017/18 prices

EDSS	UK MS costs (2011/12)	SPMS health state costs (£)
0	1,217	1,301
1	1,254	1,340
2	1,002	1,071
3	4,079	4,360
4	2,138	2,285
5	3,409	3,644
6	4,444	4,750
7	11,185	11,955
8	26,793	28,637
9	21,502	22,982

EDSS, expanded disability status scale; SPMS, secondary progressive multiple sclerosis

5.4.2 Probabilistic sensitivity analysis

The ERG re-ran the PSA by making changes to the company's base-case values and assumptions. The results of the 1000 simulations representing the incremental costs and benefits between siponimod and interferon β-1b were plotted on an incremental cost-effectiveness plane ([redacted] 13), then on a CEAC ([redacted] 14).

5.4.3 Additional deterministic analyses

We undertook additional deterministic scenario analyses, where amendments were made to the ERG's base-case, to explore the impact of these changes to our base-case results.

We undertook the following scenarios:

- Natural history transition probabilities based on the EXPAND trial[2]and London Ontario dataset[11] obtained from recent technology appraisals

- Natural history transition probabilities based on the London Ontario dataset[11] obtained from recent technology appraisals

Recent technology appraisals in DMTs for treating people with RRMS have included people who subsequently progressed to SPMS. These models assumed that on progression to SPMS, people received best supportive care, where their transitions were based on the transition matrix derived

from the London Ontario dataset. Table 71 presents the transition matrix obtained from recent appraisals and assessments.[35]

Table 71. Natural history matrix based on information from the London Ontario database11 (obtained from previous appraisals35)

EDSS From/to		EDSS state (to)										
		0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
EDSS state (from)	**0**	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
	1	0.000	0.769	0.153	0.076	0.000	0.000	0.000	0.000	0.000	0.000	0.000
	2	0.000	0.000	0.635	0.271	0.062	0.023	0.007	0.000	0.000	0.000	0.000
	3	0.000	0.000	0.000	0.629	0.252	0.076	0.033	0.002	0.005	0.000	0.000
	4	0.000	0.000	0.000	0.000	0.485	0.350	0.138	0.007	0.018	0.000	0.000
	5	0.000	0.000	0.000	0.000	0.000	0.632	0.317	0.022	0.026	0.002	0.000
	6	0.000	0.000	0.000	0.000	0.000	0.000	0.763	0.190	0.044	0.002	0.000
	7	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.804	0.189	0.006	0.000
	8	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.925	0.074	0.000
	9	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	1.000	0.000
	1	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	1.000

EDSS, expanded disability status scale

- Comparison between siponimod versus BSC (non-MAIC), using the source of natural history disability progression from EXPAND[2] and London Ontario database[11]

This scenario analysis draws on the clinical effectiveness results obtained from the EXPAND trial.[2] To our knowledge, the company's economic model allows for a comparison of siponimod versus BSC by using the non-MAIC treatment efficacy for disability progression and relapses. The HR for 6-month CDP for siponimod versus BSC is 0.740 (95% CI: 0.60, 0.920). The ERG consider this analyses important given the uncertainty in the results from the MAIC and the lack of transparency due to the unavailability of the IPD (see Section 4.4).

- Comparison between siponimod versus best supportive care (non-MAIC), using the source of natural history disability progression from London Ontario database[11] derived by the company

- Comparison between siponimod versus best supportive care (non-MAIC), using the source of natural history disability progression from London Ontario database[11] as presented in previous appraisals

The results of these exploratory analyses are presented in Table 72.

5.5 Conclusions of the cost-effectiveness section

The CS is based on a Markov model used to depict the experience of people living with SPMS. The economic model is used to evaluate the cost-effectiveness of siponimod versus DMTs used outside of their MA for the treatment of SPMS. The company's base-case compared siponimod against interferon β-1b. The model captured the clinical (CDP, ARR, AE), as well as the economic outcomes for this patient population, by incorporating clinical effectiveness information from relevant trials (see Section 5.2, ERG critique of company SLR).

The clinical effectiveness information was based on a MAIC analysis to derive the treatment effect of siponimod versus interferon β-1b in the absence of trials that directly compared these two DMTs. The model required information from a natural history cohort to show the movement/transitions of people between EDSS, which was derived from the EXPAND trial[2] and London Ontario database.[11] The costs included in the model related to the health state management costs, drug acquisition, subsequent monitoring costs, and costs associated with the treatment of AE. To have a workable economic model, the company made assumptions, most of which the ERG consider to be plausible.

The company's base-case results are based on applying a discount of [redacted] and [redacted] in the form of a PAS for siponimod and interferon β-1b (Extavia ®), respectively. The company reported an ICER of approximately [redacted] per QALY. PSA results (taken from the economic model) showed that there was a [redacted] probability that siponimod compared to interferon β-1b was cost-effective at a WTP threshold of £30,000 per QALY. One-way sensitivity analysis results demonstrated that the model was most sensitive to the HR for CDP for siponimod.

The ERG have not identified any major errors in the economic model. However, there were concerns with some inputs and assumptions made, which could potentially lead to a change to the company's base-case ICER:

1. The transition matrix derived from the EXPAND trial[2] and London Ontario dataset[11] showed that there was a probability associated with a reduction to disability. The ERG consider it to be more appropriate to use the transition matrix derived from the London Ontario dataset[11] alone, as there is a zero probability of regressing.
2. The ERG noted that the matrix derived from the London Ontario dataset[11] alone is not consistent with other SPMS-SPMS matrices used in previous appraisals.[35]

3. Using the exponential parametric curve to model the proportion of people who discontinued treatment to be plausible based on visual inspection, AIC and clinical validity
4. The health state utility values derived from the EXPAND trial[2] may not be representative to an SPMS population, due to the low number of people in each EDSS level. Therefore, the ERG consider that the health state utility values obtained from Orme et al, (2007)[12] are more appropriate.
5. The assumption that disease management costs for SPMS are the same as for people living with RRMS.

The driver of the economic model was the HR for CDP for siponimod. Due to the considerable uncertainty surrounding the MAIC and lack of transparency of the data used to estimate this relative treatment effect, the ERG would have welcomed functionality in the model to allow for a comparison between interferon β-1b and BSC, using the non-MAIC results.

6 IMPACT OF ADDITIONAL CLINICAL AND ECONOMIC ANALYSES UNDERTAKEN BY THE ERG

6.1 Impact of ERG changes on the company's base-case results

This section reports the results and the impact of the changes made to the inputs or assumptions outline in Section 5.5, which were executed one at a time (Table 72).

Table 72. Results of the ERG's exploratory analysis for the comparison between siponimod and interferon β-1b

Scenario	Siponimod			Interferon β-1b			ICER	% change
	Total LYs	Total QALYs	Total costs	Total LYs	Total QALYs	Total costs		
Base-case	16.16	4.49	[redacted]	15.86	3.17	[redacted]	[redacted]	-
Source of disability progression and relapse effectiveness estimates from ERG NMA	15.97	3.71	[redacted]	15.86	3.17	[redacted]	[redacted]	253.36%
Source of natural history, London Ontario database[11]	15.80	3.20	[redacted]	15.58	2.08	[redacted]	[redacted]	17.25%
Exponential parametric curve fitted to discontinuation data (and time constant discontinuation rates)	16.27	4.88	[redacted]	15.87	3.18	[redacted]	[redacted]	12.98%
Treatment effect applied as a rate	16.14	4.43	[redacted]	15.86	3.16	[redacted]	[redacted]	6.55%
Health state utility values from Orme et al (2007)[12]	16.16	3.25	[redacted]	15.86	2.08	[redacted]	[redacted]	13.17%
Cost of £35 for genotyping borne by the company	16.16	4.49	[redacted]	15.86	3.17	[redacted]	[redacted]	-0.14%
Health state management costs obtained from TA320[18]	16.16	4.49	[redacted]	15.86	3.17	[redacted]	[redacted]	0.42%

ICER, incremental cost-effectiveness ratio; LY, life-years; QALY, quality adjusted life-years; TA, technology appraisal

The ERG's exploratory results presented in Table 72 demonstrates that changing the source of disability progression and relapse effectiveness to the results of the ERG's NMA had the greatest impact to the company's base-case ICER, with an increase by 253.36%. Changing the natural history transition probabilities derived from the EXPAND trial and London Ontario database to London Ontario only reduced the QALYs yielded across DMTs; indicating that there was additional QALY benefit generated when regressions were allowed despite there being no direct impact/treatment effect on backward transition probabilities. This change resulted in an increase of 17.25% to the company's base-case ICER.

Table 73 presents the results for changing transition probabilities for the natural history cohort. Using the transition probabilities derived from the EXPAND trial[2] supplemented with those from previous technology appraisals/assessments had the greatest impact to the company's base-case results, increasing the ICER from approximately [redacted] to [redacted] per QALY.

Table 74 reports the ERG's exploratory analysis results based on the comparison between siponimod versus BSC. These results show that using the non-MAIC results for CDP6M and ARR, resulted in an ICER of approximately [redacted] per QALY. Using the non-MAIC results in addition to making a change to the natural history cohort resulted in an ICER of approximately [redacted] per QALY gained.

Impact of additional deterministic analyses undertaken by the ERG for the comparison between siponimod and interferon β-1b

The impact of the additional deterministic analysis we conducted in presented in Table 73 and Table 74.

Table 73. Results of additional deterministic analysis for the comparison between siponimod and interferon β-1b

Scenario	Siponimod			Interferon β-1b (Extavia ®)			ICER	% change
	Total LYs	Total QALYs	Total costs	Total LYs	Total QALYs	Total costs		
Base-case	16.16	4.49	[redacted]	15.86	3.17	[redacted]	[redacted]	-
Source of natural history, EXPAND and London Ontario database[11] (TPs obtained from recent TAs)	15.95	4.49	[redacted]	15.60	3.16	[redacted]	[redacted]	21.30%
Source of natural history, London Ontario database[11] (TPs obtained from recent TAs)	15.33	2.39	[redacted]	15.08	1.27	[redacted]	[redacted]	16.77%

BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LY, life-years; QALY, quality adjusted life-years; TA, technology appraisal

Table 74. Results of additional deterministic analysis for the comparison between siponimod and BSC

Scenario	Siponimod			Best supportive care			ICER
	Total LYs	Total QALYs	Total costs	Total LYs	Total QALYs	Total costs	
Siponimod versus BSC (non-MAIC), natural history disability progression from EXPAND and London Ontario database[11]	15.97	3.71	[redacted]	15.81	3.01	[redacted]	[redacted]
Siponimod versus BSC (non-MAIC), natural history disability progression from London Ontario database[11] derived by the company	15.66	2.54	[redacted]	15.55	1.96	[redacted]	[redacted]
Siponimod versus BSC (non-MAIC), natural history disability progression from London Ontario database[11] as presented in previous appraisals	15.17	1.70	[redacted]	15.05	1.15	[redacted]	[redacted]
Siponimod versus BSC (non-MAIC), natural history, EXPAND and London Ontario database[11] (TPs obtained from recent TAs)	15.73	3.71	[redacted]	15.54	3.01	[redacted]	[redacted]

BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LY, life-years; MAIC, matched-adjusting indirect comparison; QALY, quality adjusted life-years; TA, technology appraisal; TP, transition probability

6.2 Results of ERG base-case analysis

The ERG's base-case analysis includes making the following changes simultaneously in the economic model for the comparison between interferon β-1b versus siponimod:

- ERG's NMA results for 6-month CDP (HR=0.80, 95% CI:0.57, 1.13) and ARR (HR=0.65, 95% CI:0.46, 1.04)
- Natural history transition probabilities based on the London Ontario dataset[11] derived by the company
- Exponential distribution fitted to discontinuation data
- Treatment effect for siponimod compared to interferon β-1b applied as a rate as opposed to a probability
- Health state utility values obtained from Orme et al, 2007[12]
- Costs of £35 for genotyping borne by the company
- Health state management costs obtained from TA320[18]

A table detailing the changes made to the company's economic model based on the ERG's amendments are presented in ERG appendix D.

6.2.1 ERG's base-case deterministic results

The ERG's base-case analysis compares siponimod versus interferon β-1b. These results are presented in Table 75, which show that treatment with siponimod was more costly and more effective than interferon β-1b, with an ICER of approximately [redacted] per QALY.

Table 75. ERG's base-case deterministic results, under PAS prices

Treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Interferon β-1b	[redacted]	15.58	1.07	-	-	-	-
Siponimod	[redacted]	15.68	1.52	[redacted]	0.10	0.4521	[redacted]

ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALYs, quality adjusted life-years; SPMS, secondary progressive multiple sclerosis

6.2.2 ERG's probabilistic sensitivity analysis results

PSA was undertaken based on the cost per QALY only. PSA results are reported in Table 76, which shows that the total QALYs yielded are in line with the deterministic results. However, the total costs are slightly underestimated in comparison to the deterministic results, which generated an ICER of approximately [redacted] per QALY.

Table 76. ERG's probabilistic sensitivity analysis results, under PAS prices

Treatment	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Interferon β-1b	[redacted]	1.06	-	-	-
Siponimod	[redacted]	1.51	[redacted]	0.45	[redacted]

ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALYs, quality adjusted life-years; SPMS, secondary progressive multiple sclerosis

PSA results are presented in the form of a scatterplot presented on an incremental cost-effectiveness plane (see [redacted] 13) and cost-effectiveness acceptability curves (see [redacted] 14). The scatterplot demonstrate that majority of the simulations are in the north-east ([redacted]) quadrant indicating that siponimod is more expensive and yields more QALYs than interferon β-1b. Additionally, [redacted] of the simulations are in the north-west quadrant indicating that treatment with siponimod is more expensive but is less effective than interferon β-1b. These results are reflected in the CEAC ([redacted] 14), which starts at zero and increases as the WTP threshold increases, but never reaches one. The PSA results suggests that at a WTP threshold of £20,000 per QALY, there is a [redacted] probability that siponimod when compared to interferon β-1b is cost-effective. At the upper end of the WTP threshold of £30,000 per QALY, there is a [redacted] probability that siponimod is cost-effective.

Figure 13. Scatterplot of DMTs on the incremental cost-effectiveness plane

Figure 14. Cost-effectiveness acceptability curve

6.2.3 ERG scenario analysis

The ERG undertook further scenario analyses for the comparison between siponimod and interferon β-1b. Each change listed below was executed one at a time, results are presented in Table 77:

- Using the results from the company's MAIC for 6-month CDP and ARR
- Using the cost of £4,357 for treating AE obtained from TA527[78] – RSS model and ScHARR analysis
- Natural history transition probabilities based on the EXPAND trial[2] and London Ontario database[11] derived by the company
- Source of caregiver disutility obtained from Acaster et al, (2013)[74]
- Natural history annualised relapse rates derived from Patzold and Pocklington (1982)[75] and UK MS Survey[12]

Table 77. Results of additional deterministic analysis for the comparison between siponimod and interferon β-1b

Scenario	Siponimod			Interferon β-1b			ICER	% change
	Total LYs	Total QALYs	Total costs	Total LYs	Total QALYs	Total costs		
Base-case	15.68	1.52	[redacted]	15.58	1.07	[redacted]	[redacted]	-
Using the results from the company's MAIC for 6-mont CDP and ARR	15.85	2.20	[redacted]	15.58	1.07	[redacted]	[redacted]	-68.31%
Adverse treatment costs (£4,357) obtained from TA527[78]	15.68	1.52	[redacted]	15.58	1.07	[redacted]	[redacted]	-1.48%
Natural history disability progression from London Ontario database[11] derived by the company	16.00	2.66	[redacted]	15.86	2.08	[redacted]	[redacted]	-12.48%
Source of caregiver disutility obtained from Acaster et al., (2013)[74]	15.68	0.63	[redacted]	15.58	0.29	[redacted]	[redacted]	31.29%
Natural history annualised relapse rates derived from Patzold and Pocklington (1982)[75] and UK MS Survey[12]	15.68	1.50	[redacted]	15.58	1.04	[redacted]	[redacted]	-1.70%

BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LY, life-years; QALY, quality adjusted life-years; TA, technology appraisal

6.2.4 ERG scenario analysis results

The direction of the ERG scenario analysis results are all in line with our expectations. The ERG's deterministic base-case result was most sensitive to the scenario that used the company's MAIC results for 6-month CDP and ARR, which reduced the ICER by approximately 68%. All other scenario analyses except using the caregiver disutility values from Acaster et al., (2013)[74] led to a reduction to the ICER. Using the Acaster disutilities led to a reduction in the QALYs across both treatments and no impact to the total costs, which resulted in a 31% increase to the ICER.

6.3 Conclusion of the cost effectiveness analysis

The company's economic analysis was based on a Markov cohort model developed in Microsoft Excel. The ERG considered the choice of the model appropriate to simulate the experience of people with SPMS, and to capture the long-term costs and benefits associated with treatment. The company compared siponimod versus interferon β-1b in the base-case analysis, which was appropriate and in line with the NICE final scope[80] for treatment of people with SPMS. The scope also included other comparators (DMTs) used outside of their MA and licensed dosing schedule (see Section 3.3 ERG critique of comparators).

The company undertook SLR of the evidence to identify information to populate the economic model. The clinical effectiveness information for siponimod and interferon β-1b was obtained from the EXPAND trial[2] and the NA study[7] (see Section 4.3.1) and costs obtained from multiple sources. The company used a MAIC approach to synthesise the clinical effectiveness evidence, and estimated the treatment effect for CDP and ARR. The ERG critiqued the company MAIC in Section 4.4.

The resource use and costs were in keeping with the perspective of the economic analysis, with information obtained from published sources and using current prices. To have a workable model the company made some simplifying assumptions, which the ERG considered to be plausible. Under the company's assumptions and the economic model used, the base-case deterministic results showed that siponimod was more expensive and more effective than interferon β-1b, resulting in an ICER of approximately [redacted] per QALY gained. PSA results demonstrated that siponimod when compared to interferon β-1b had a [redacted] probability of being cost-effective at a WTP threshold of £30,000 per QALY.

The ERG made some amendments to the company's economic model inputs, which formed the basis for the ERG's base-case model. These changes resulted in differences between the company's base-case results and those reported by the ERG. The company's base-case results were presented based on using the PAS price in the form of a discount on the costs for all DMTs, and this was the approach taken in the ERG's analysis.

The ERG highlighted several concerns and uncertainties in the model input, which suggest that the company's cost-effectiveness results could potentially be overestimated. The ERG's amendments using alternative sources of information or assumptions included the following:

- ERG's NMA results for 6-month CDP (HR=0.80, 95% CI:0.57, 1.13) and ARR (HR=0.65, 95% CI:0.46, 1.04)
- Natural history transition probabilities based on the London Ontario dataset[11]derived by the company
- Exponential distribution fitted to discontinuation data
- Treatment effect for siponimod compared to interferon β-1b applied as a rate as opposed to a probability
- Health state utility values obtained from Orme et al, 2007[12]
- Costs of £35 for genotyping borne by the company
- Health state management costs obtained from TA320[18]

Based on the ERG's preferred inputs and assumptions changed simultaneously, the results demonstrate that siponimod compared to interferon β-1b was more expensive but yielded more QALYs, resulting in an ICER of approximately [redacted] per QALY. PSA results demonstrated that at a WTP threshold of £30,000 per QALY siponimod had a [redacted] probability of being cost-effective.

7 END OF LIFE

The company have not presented any end of life considerations in the CS.

8 OVERALL CONCLUSION

8.1 Clinical effectiveness

The clinical effectiveness section of the CS is based on a SLR, which included six randomised controlled trials (RCT) conducted in patients with SPMS.[2, 4-10] The EXPAND[2] double-blind phase-III placebo-controlled randomised trial was the pivotal trial which assessed the effectiveness and safety of siponimod. In EXPAND,[2] siponimod displayed a significant improvement compared with placebo for 6-month CDP (HR=0.74; 95% CI: 0.60, 0.92) and ARR (HR= 0.45; 95% CI: 0.34, 0.59), the key model inputs for the economic base-case.

The company provided a MAIC analysis to indirectly compare the effectiveness of siponimod and other therapies licensed and/or used in the treatment of SPMS in clinical practice. The ERG consider that the interpretation of findings presented from MAIC should be interpreted with caution, due to unaccounted for cross-trial heterogeneity in population characteristics, a small ESS, limited relevance of the comparator treatment trial populations and limited applicability of results to the target populations of patients with active SPMS.

The ERG performed exploratory NMA for 3-month CDP, 6-month CDP and ARR. The ERG NMA estimates generally favour siponimod over the comparator treatments, however the results of the NMA are not statistically significant with the exception of siponimod versus SC interferon β-1a 44 μg for the 3-month CDP outcome (HR 0.79 95% CI 0.66, 0.95) and siponimod versus SC interferon β-1a 22 μg and 44 μg for the ARR outcome ([RR 0.65 95% CI 0.47, 0.91], [RR 0.65 95%CI 0.46, 0.92]). The results of the ERG NMA for 6-month CDP and ARR formed the basis for the ERG's base-case model.

8.2 Cost effectiveness

The company undertook SLR of the evidence to identify information to populate the economic model. The company's economic analysis was based on a Markov cohort model developed in Microsoft Excel. The ERG considered the choice of the model appropriate to simulate the experience of people with SPMS, and to capture the long-term costs and benefits associated with treatment. The company compared siponimod versus interferon β-1b in the base-case analysis. The ERG considered this to be appropriate and in line with the NICE final scope[80] for treatment of people with SPMS.

The company base-case deterministic results suggested that siponimod was more expensive and more effective than interferon β-1b. The CS reported an ICER of approximately [redacted] per QALY gained. PSA results signified that siponimod had a [redacted] probability of being cost-effective at a WTP threshold of £30,000 per QALY when compared to interferon β-1b.

The ERG notes several uncertainties in the model input. When the ERG's preferred inputs and assumptions were changed simultaneously, the ERG base-case results demonstrate that siponimod was more expensive but yielded more QALYs when compared to interferon β-1b. This resulted in an ICER of approximately [redacted] per QALY. The EGR PSA results suggest that at a WTP threshold of £30,000 per QALY siponimod had a [redacted] probability of being cost-effective.

8.3 Overall summary

The company's submission draws on the clinical evidence from two main trials, the EXPAND trial and the North American Study, with both including participants with SPMS. The EXPAND trial compared interferon β-1b versus placebo, while the North American Study compared siponimod versus placebo. The primary outcomes included in both trials were 6-month confirmed disability progression and annualised relapse rates.

The company provided rationale for using the MAIC methodology to derive the treatment effectiveness as opposed to other methods to synthesise the clinical evidence. Several concerns were raised in this submission, with majority related to the MAIC and the lack of transparency. Hence, the findings from the economic analysis which draws heavily on these results should be interpreted with caution, due to unaccounted cross-trial heterogeneity in characteristics of populations, small ESS, limited relevance of the comparator treatment trials' populations, applicability of results to the target populations of patients with active SPMS and lack of independent assessment of the IPD by the ERG. Additionally, there are several uncertainties with respect to the clinical evidence that compares siponimod to other DMTs used outside of their marketing authorisation, which will limit any economic analysis comparing these DMTs.

9 REFERENCES

1. *Drug Approval Package: Mayzent (siponimod)*. U.S. Food and Drug Administration; 2019. URL: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/209884Orig1s000TOC.cfm (Accessed 16/10/2019).
2. Kappos L, Bar-Or A, Cree BAC, Fox RJ, Giovannoni G, Gold R, *et al.* Siponimod versus placebo in secondary progressive multiple sclerosis (EXPAND): a double-blind, randomised, phase 3 study. *Lancet* 2018;**391**(10127):1263-73. http://dx.doi.org/10.1016/s0140-6736(18)30475-6
3. Lublin FD, Reingold SC, Cohen JA, Cutter GR, Sorensen PS, Thompson AJ, *et al.* Defining the clinical course of multiple sclerosis: the 2013 revisions. *Neurology* 2014;**83**(3):278-86. http://dx.doi.org/10.1212/wnl.0000000000000560
4. Kapoor R, Ho PR, Campbell N, Chang I, Deykin A, Forrestal F, *et al.* Effect of natalizumab on disease progression in secondary progressive multiple sclerosis (ASCEND): a phase 3, randomised, double-blind, placebo-controlled trial with an open-label extension. *Lancet Neurol* 2018;**17**(5):405-15. http://dx.doi.org/10.1016/s1474-4422(18)30069-3
5. SPECTRIMS MS Study Group. Randomized controlled trial of interferon- beta-1a in secondary progressive MS: Clinical results. *Neurology* 2001;**56**(11):1496-504.
6. Li DK, Zhao GJ, Paty DW. Randomized controlled trial of interferon-beta-1a in secondary progressive MS: MRI results. *Neurology* 2001;**56**(11):1505-13.
7. 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.
8. European Study Group. 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* 1998;**352**(9139):1491-7.
9. Kappos L, Polman C, Pozzilli C, Thompson A, Beckmann K, Dahlke F. Final analysis of the European multicenter trial on IFNbeta-1b in secondary-progressive MS. *Neurology* 2001;**57**(11):1969-75.
10. Cohen JA, Cutter GR, Fischer JS, Goodman AD, Heidenreich FR, Kooijmans MF, *et al.* Benefit of interferon beta-1a on MSFC progression in secondary progressive MS. *Neurology* 2002;**59**(5):679-87.
11. Weinshenker BG, Bass B, Rice GP, Noseworthy J, Carriere W, Baskerville J, *et al.* The natural history of multiple sclerosis: a geographically based study. I. Clinical course and disability. *Brain* 1989;**112 (Pt 1)**:133-46. http://dx.doi.org/10.1093/brain/112.1.133
12. Orme M, Kerrigan J, Tyas D, Russell N, Nixon R. The effect of disease, functional status, and relapses on the utility of people with multiple sclerosis in the UK. *Value Health* 2007;**10**(1):54-60. http://dx.doi.org/10.1111/j.1524-4733.2006.00144.x
13. Office for National Statistics. *National life tables, United Kingdom. 2015-2017*. 2017. URL: https://www.ons.gov.uk/file?uri=/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/datasets/nationallifetablesunitedkingdomreferencetables/current/nltuk1517reg.xls (Accessed 12 April 2019).
14. Pokorski RJ. Long-term survival experience of patients with multiple sclerosis. *J Insur Med* 1997;**29**(2):101-6.
15. *BNF 77 [online]*. London: BMJ Group, Pharmaceutical Press; 2019. URL: https://bnf.nice.org.uk/ (Accessed 31 May 2019).
16. Curtis L, Burns A. *PSSRU Unit Costs of Health and Social Care*. 2018. URL: https://kar.kent.ac.uk/70995/ (Accessed 15 April 2019).
17. Department of Health. *NHS reference costs 2017/18*. 2018. URL: https://improvement.nhs.uk/documents/1973/2_-_National_schedule_of_reference_costs_v2.xlsx (Accessed 15 April 2019).
18. National Institute for Health and Care Excellence (NICE). *Dimethyl fumarate for treating relapsing-remitting multiple sclerosis. Technology appraisal guidance [TA320]*. 2014. URL: https://www.nice.org.uk/guidance/ta320 (Accessed 12 April 2019).

19. Melendez-Torres GJ, Auguste P, Armoiry X, Maheswaran H, Court R, Madan J*, et al.* Clinical effectiveness and cost-effectiveness of beta-interferon and glatiramer acetate for treating multiple sclerosis: systematic review and economic evaluation. *Health Technol Assess* 2017;**21**(52):1-352. http://dx.doi.org/10.3310/hta21520
20. Lublin FD, Reingold SC. Defining the clinical course of multiple sclerosis: results of an international survey. National Multiple Sclerosis Society (USA) Advisory Committee on Clinical Trials of New Agents in Multiple Sclerosis. *Neurology* 1996;**46**(4):907-11.
21. Multiple Sclerosis Trust. *Is MS care fair? Key findings from the MS Trust's survey into the experiences of people living with MS*. 2016. URL: https://www.mstrust.org.uk/sites/default/files/MS%20care%20media%20report%20a4.pdf (Accessed 16 October 2019).
22. Compston A, Coles A. Multiple sclerosis. *Lancet* 2008;**372**(9648):1502-17. http://dx.doi.org/10.1016/s0140-6736(08)61620-7
23. Multiple Sclerosis International Federation. *Atlas of MS 2013: Mapping multiple sclerosis around the world. http://www.msif.org/wp-content/uploads/2014/09/Atlas-of-MS.pdf. Accessed 16-Oct-2019*; 2013.
24. Simpson Jr S, Mina S, Morris H, Mahendran S, Taylor B, Boggild M. The epidemiology of multiple sclerosis in the Isle of Man: 2006–2011. *Acta Neurologica Scandinavica* 2015;**132**(6):381-8. http://dx.doi.org/10.1111/ane.12405
25. Mackenzie IS, Morant SV, Bloomfield GA, MacDonald TM, O'Riordan J. Incidence and prevalence of multiple sclerosis in the UK 1990-2010: a descriptive study in the General Practice Research Database. *J Neurol Neurosurg Psychiatry* 2014;**85**(1):76-84. http://dx.doi.org/10.1136/jnnp-2013-305450
26. MS Society. *MS in the UK*. 2018. URL: https://www.mssociety.org.uk/care-and-support/resources-and-publications/publications-search/ms-in-the-uk (Accessed 16 October 2019).
27. Flachenecker P, Kobelt G, Berg J, Capsa D, Gannedahl M. New insights into the burden and costs of multiple sclerosis in Europe: Results for Germany. *Multiple Sclerosis Journal* 2017;**23**(2_suppl):78-90. http://dx.doi.org/10.1177/1352458517708141
28. Bakshi R, Thompson AJ, Rocca MA, Pelletier D, Dousset V, Barkhof F*, et al.* MRI in multiple sclerosis: current status and future prospects. *Lancet Neurol* 2008;**7**(7):615-25. http://dx.doi.org/10.1016/s1474-4422(08)70137-6
29. Thompson AJ, Banwell BL, Barkhof F, Carroll WM, Coetzee T, Comi G*, et al.* Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *Lancet Neurol* 2018;**17**(2):162-73. http://dx.doi.org/10.1016/s1474-4422(17)30470-2
30. Multiple Sclerosis Trust. *Expanded Disability Status Scale (EDSS)*. 2018. URL: https://www.mstrust.org.uk/a-z/expanded-disability-status-scale-edss (Accessed 16 October 2019).
31. La Mantia L, Vacchi L, Rovaris M, Di Pietrantonj C, Ebers G, Fredrikson S*, et al.* Interferon beta for secondary progressive multiple sclerosis: a systematic review. *J Neurol Neurosurg Psychiatry* 2013;**84**(4):420-6. http://dx.doi.org/10.1136/jnnp-2012-303291
32. NHS England. *Treatment Algorithm for Multiple Sclerosis Disease-modifying Therapies*. 2019. URL: https://www.engage.england.nhs.uk/consultation/specialised-services-algorithm/user_uploads/treatment-algorithm-with-notes-v9.pdf (Accessed 08 March 2019).
33. Gergely P, Nuesslein-Hildesheim B, Guerini D, Brinkmann V, Traebert M, Bruns C*, et al.* The selective sphingosine 1-phosphate receptor modulator BAF312 redirects lymphocyte distribution and has species-specific effects on heart rate. *Br J Pharmacol* 2012;**167**(5):1035-47. http://dx.doi.org/10.1111/j.1476-5381.2012.02061.x
34. Scott FL, Clemons B, Brooks J, Brahmachary E, Powell R, Dedman H*, et al.* Ozanimod (RPC1063) is a potent sphingosine-1-phosphate receptor-1 (S1P1) and receptor-5 (S1P5) agonist with autoimmune disease-modifying activity. *Br J Pharmacol* 2016;**173**(11):1778-92. http://dx.doi.org/10.1111/bph.13476

35. Institute for Clinical and Economic Review (ICER). *Siponimod for the Treatment of Secondary Progressive Multiple Sclerosis: Effectiveness and Value*. 2019. URL: https://icer-review.org/wp-content/uploads/2018/10/ICER_MS_Evidence_Report_050219.pdf (Accessed 11 June 2019).
36. Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, *et al.* The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;**343**:d5928. http://dx.doi.org/10.1136/bmj.d5928
37. Scolding N, Barnes D, Cader S, Chataway J, Chaudhuri A, Coles A, *et al.* Association of British Neurologists: revised (2015) guidelines for prescribing disease-modifying treatments in multiple sclerosis. *Pract Neurol* 2015;**15**(4):273-9. http://dx.doi.org/10.1136/practneurol-2015-001139
38. National Institute for Health and Care Excellence (NICE). *Daclizumab for treating relapsing–remitting multiple sclerosis Technology appraisal 441 [TA441]*. 2017. URL: https://www.nice.org.uk/guidance/ta441 (Accessed 6 June 2019).
39. Tourbah A, Lebrun-Frenay C, Edan G, Clanet M, Papeix C, Vukusic S, *et al.* MD1003 (high-dose biotin) for the treatment of progressive multiple sclerosis: A randomised, double-blind, placebo-controlled study. *Mult Scler* 2016;**22**(13):1719-31. http://dx.doi.org/10.1177/1352458516667568
40. Chataway J, Schuerer N, Alsanousi A, Chan D, MacManus D, Hunter K, *et al.* Effect of high-dose simvastatin on brain atrophy and disability in secondary progressive multiple sclerosis (MS-STAT): a randomised, placebo-controlled, phase 2 trial. *Lancet* 2014;**383**(9936):2213-21. http://dx.doi.org/10.1016/s0140-6736(13)62242-4
41. Morales IB, Eleftheriou E, Maranda L, Politi L, Ionete C. The safety and efficacy of Rituximab Use in Secondary-Progressive Multiple Sclerosis (SPMS) at UMMHC: five years follow up data. 2017;**88**(16 Supplement):P5.408.
42. Perrone C, Berriosmorales I, Beretich B, Riskind P, Ionete C. Rituximab in the treatment of secondary-progressive multiple sclerosis. *Multiple Sclerosis Journal* 2014;**20**:194.
43. Gunduz T, Ozcan G, Çakar A, Akçay H, Acarli AO, Kürtüncü M, *et al.* Comparison of Mitoxantrone versus cyclophosphamide in patients with secondary progressive multiple sclerosis. *European Journal of Neurology* 2016;**23**.
44. Perini P, Calabrese M, Tiberio M, Ranzato F, Battistin L, Gallo P. Mitoxantrone versus cyclophosphamide in secondary-progressive multiple sclerosis: a comparative study. *J Neurol* 2006;**253**(8):1034-40. http://dx.doi.org/10.1007/s00415-006-0154-7
45. Mostert J, Heersema T, Mahajan M, Van Der Grond J, Van Buchem MA, De Keyser J. The effect of fluoxetine on progression in progressive multiple sclerosis: a double-blind, randomized, placebo-controlled trial. *ISRN Neurol* 2013;**2013**:370943. http://dx.doi.org/10.1155/2013/370943
46. Vermersch P, Benrabah R, Schmidt N, Zephir H, Clavelou P, Vongsouthi C, *et al.* Masitinib treatment in patients with progressive multiple sclerosis: a randomized pilot study. *BMC Neurol* 2012;**12**:36. http://dx.doi.org/10.1186/1471-2377-12-36
47. Rice GP, Filippi M, Comi G. Cladribine and progressive MS: clinical and MRI outcomes of a multicenter controlled trial. Cladribine MRI Study Group. *Neurology* 2000;**54**(5):1145-55. http://dx.doi.org/10.1212/wnl.54.5.1145
48. Fernandez O, Izquierdo G, Fernandez V, Leyva L, Reyes V, Guerrero M, *et al.* Adipose-derived mesenchymal stem cells (AdMSC) for the treatment of secondary-progressive multiple sclerosis: A triple blinded, placebo controlled, randomized phase I/II safety and feasibility study. *PLoS One* 2018;**13**(5):e0195891. http://dx.doi.org/10.1371/journal.pone.0195891
49. Bosco A, Cazzato G, Monti F, Antonello RM, Torre P. Double-blind, placebo-controlled, randomized study of idebenone in patients with chronic progressive MS. Paper presented at ECTRIMS 13th Congress of the European Committee for Treatment and Research in Multiple Sclerosis. Istanbul, Turkey, 2-5 November 1997. *Multiple Sclerosis* 1997;**3**:349 [Abstract number P251].
50. Beutler E, Sipe JC, Romine JS, Koziol JA, McMillan R, Zyroff J. The treatment of chronic progressive multiple sclerosis with cladribine. *Proc Natl Acad Sci U S A* 1996;**93**(4):1716-20. http://dx.doi.org/10.1073/pnas.93.4.1716

51. Bornstein MB, Miller A, Slagle S, Weitzman M, Drexler E, Keilson M, *et al.* A placebo-controlled, double-blind, randomized, two-center, pilot trial of Cop 1 in chronic progressive multiple sclerosis. *Neurology* 1991;**41**(4):533-9. http://dx.doi.org/10.1212/wnl.41.4.533
52. Miller DH, Khan OA, Sheremata WA, Blumhardt LD, Rice GP, Libonati MA, *et al.* A controlled trial of natalizumab for relapsing multiple sclerosis. *N Engl J Med* 2003;**348**(1):15-23. http://dx.doi.org/10.1056/NEJMoa020696
53. Patti F, L'Episcopo MR, Cataldi ML, Reggio A. Natural interferon-beta treatment of relapsing-remitting and secondary-progressive multiple sclerosis patients. A two-year study. *Acta Neurol Scand* 1999;**100**(5):283-9. http://dx.doi.org/10.1111/j.1600-0404.1999.tb00397.x
54. Wang L, Qi CH, Zhong R, Yuan C, Zhong QY. Efficacy of alemtuzumab and natalizumab in the treatment of different stages of multiple sclerosis patients. *Medicine (Baltimore)* 2018;**97**(8):e9908. http://dx.doi.org/10.1097/md.0000000000009908
55. Andersen O, Elovaara I, Farkkila M, Hansen HJ, Mellgren SI, Myhr KM, *et al.* Multicentre, randomised, double blind, placebo controlled, phase III study of weekly, low dose, subcutaneous interferon beta-1a in secondary progressive multiple sclerosis. *J Neurol Neurosurg Psychiatry* 2004;**75**(5):706-10.
56. Bucher HC, Guyatt GH, Griffith LE, Walter SD. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. *J Clin Epidemiol* 1997;**50**(6):683-91. http://dx.doi.org/10.1016/s0895-4356(97)00049-8
57. Phillippo DM, Ades AE, Dias S, Palmer S, Abrams KR, Welton NJ. *NICE DSU Technical Support Document 18: Methods for Population-Adjusted Indirect Comparisons in Submissions to NICE*. Sheffield: Decision Support Unit, ScHARR, University of Sheffield; 2016. URL: http://nicedsu.org.uk/wp-content/uploads/2018/08/Population-adjustment-TSD-FINAL-ref-rerun.pdf (Accessed 22 March 2019).
58. Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. *Stat Med* 2009;**28**(25):3083-107. http://dx.doi.org/10.1002/sim.3697
59. Signorovitch J, Swallow E, Kantor E, Wang X, Klimovsky J, Haas T, *et al.* Everolimus and sunitinib for advanced pancreatic neuroendocrine tumors: a matching-adjusted indirect comparison. *Exp Hematol Oncol* 2013;**2**(1):32. http://dx.doi.org/10.1186/2162-3619-2-32
60. National Institute for Health and Care Excellence (NICE). *Cladribine tablets for treating relapsing-remitting multiple sclerosis. Technology appraisal guidance [TA493]*. 2017. URL: https://www.nice.org.uk/Guidance/TA493 (Accessed 6 March 2019).
61. Inojosa H, Proschmann U, Akgun K, Ziemssen T. A focus on secondary progressive multiple sclerosis (SPMS): challenges in diagnosis and definition. *J Neurol* 2019. http://dx.doi.org/10.1007/s00415-019-09489-5
62. Lorscheider J, Buzzard K, Jokubaitis V, Spelman T, Havrdova E, Horakova D, *et al.* Defining secondary progressive multiple sclerosis. *Brain* 2016;**139**(Pt 9):2395-405. http://dx.doi.org/10.1093/brain/aww173
63. *Stata*. Texas, USA: StataCorp LLC. URL: https://www.stata.com/ (Accessed 10 October 2019).
64. PharmaTimes Website. *Novartis gets approval to sell interferon beta-1b in Europe*. 2008. URL: http://www.pharmatimes.com/news/novartis_gets_approval_to_sell_interferon_beta-1b_in_europe_986982 (Accessed 9 October 2019).
65. National Institute for Health and Care Excellence (NICE). *Guide to the methods of technology appraisal 2013*. 2013. URL: http://www.nice.org.uk/process/pmg9 (Accessed 26 April 2019).
66. National Institute for Health and Clinical Excellence (NICE). *Natalizumab for the treatment of adults with highly active relapsing-remitting multiple sclerosis. Technology appraisal guidance [TA127]*. 2007. URL: https://www.nice.org.uk/guidance/ta127 (Accessed 12 April 2019).
67. Drummond M, Jefferson T. Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. *BMJ* 1996;**313**:275.

68. 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):611-34. http://dx.doi.org/10.1016/S0149-2918(03)80100-5
69. Kobelt G, Jönsson L, Henriksson F, Fredrikson S, Jönsson B. Cost-utility analysis of interferon beta-1b in secondary progressive multiple sclerosis. *International Journal of Technology Assessment in Health Care* 2000;**16**(3):768-80.
70. Kobelt G, Jönsson L, Miltenburger C, Jönsson B. Cost-utility analysis of interferon beta-1b in secondary progressive multiple sclerosis using natural history disease data. *International Journal of Technology Assessment in Health Care* 2002;**18**(1):127-38.
71. 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 Transplant* 2010;**45**(6):1014-21. http://dx.doi.org/10.1038/bmt.2009.305
72. Forbes RB, Lees A, Waugh N, Swingler RJ. Population based cost utility study of interferon beta-1b in secondary progressive multiple sclerosis. *British Medical Journal* 1999;**319**(7224):1529-33.
73. Hawton A, Green C. Health Utilities for Multiple Sclerosis. *Value Health* 2016;**19**(4):460-8. http://dx.doi.org/10.1016/j.jval.2016.01.002
74. Acaster S, Perard R, Chauhan D, Lloyd AJ. A forgotten aspect of the NICE reference case: an observational study of the health related quality of life impact on caregivers of people with multiple sclerosis. *BMC Health Services Research* 2013;**13**(1):346. http://dx.doi.org/10.1186/1472-6963-13-346
75. Patzold U, Pocklington PR. Course of multiple sclerosis. First results of a prospective study carried out of 102 MS patients from 1976-1980. *Acta Neurol Scand* 1982;**65**(4):248-66.
76. Ruutiainen J, Viita AM, Hahl J, Sundell J, Nissinen H. Burden of illness in multiple sclerosis (DEFENSE) study: the costs and quality-of-life of Finnish patients with multiple sclerosis. *J Med Econ* 2016;**19**(1):21-33. http://dx.doi.org/10.3111/13696998.2015.1086362
77. Gani R, Giovannoni G, Bates D, Kemball B, Hughes S, Kerrigan J. Cost-effectiveness analyses of natalizumab (Tysabri) compared with other disease-modifying therapies for people with highly active relapsing-remitting multiple sclerosis in the UK. *Pharmacoeconomics* 2008;**26**(7):617-27. http://dx.doi.org/10.2165/00019053-200826070-00008
78. National Institute for Health and Care Excellence (NICE). *Beta interferons and glatiramer acetate for treating multiple sclerosis. Technology appraisal guidance [TA527]*. 2018. URL: https://www.nice.org.uk/guidance/ta527 (Accessed 6 March 2019).
79. Tyas D, Kerrigan J, Russell N, Nixon R. The distribution of the cost of multiple sclerosis in the UK: how do costs vary by illness severity? *Value Health* 2007;**10**(5):386-9. http://dx.doi.org/10.1111/j.1524-4733.2007.00192.x
80. National Institute for Health and Care Excellence (NICE). *Siponimod for treating secondary progressive multiple sclerosis: Final scope*. 2019. URL: https://www.nice.org.uk/guidance/gid-ta10436/documents/final-scope (Accessed 6 September 2019).

10 APPENDICES

10.1 ERG appendix A

Trials characteristics of studies included in the indirect treatment comparisons.

SPECTRIMS study

SPECTRIMS was a multicentre, phase III randomised clinical trial where 618 patients with SPMS were randomly assigned to receive either IFNβ-1a 22 μg or IFNβ-1a 44 μg of or placebo, injected subcutaneously over 3 years. At baseline, the proportion of females, mean EDSS score, duration of MS and duration of SPMS were comparable (differences <10%). The patients in the SPECTRIMS study were younger than that of EXPAND (42.8 vs 48.0 years), a lower proportion of these patients were relapse-free in the 2 years prior to the study (53% vs 64%), but they had a higher mean number of relapses per patients in the previous 2 years (0.9 vs 0.7). The remaining baseline characteristics reported in EXPAND were not reported in SPECTRIMS. The primary outcome was time to confirmed progression in disability, defined as increase from baseline by at least 1 EDSS point, or 0.5 point if baseline EDSS was ≥ 5.5, confirmed 3 months later with no intervening score lower than the minimum required level, and ARR and discontinuation were key secondary outcomes. Time to confirmed 3-month CDP was not significantly affected by treatment (HR=0.83; 95% CI: 0.65 to 1.07; p=0.146, for the 44 μg group). Relapse rate was reduced from 0.71 per year to 0.50 per year with both treatments (p<0.001 for both). Statistical analyses were based on the Cox proportional hazards (PH) model and log-rank tests. The ERG considers this approach to trial statistics appropriate, and also agree with the company's assessment of SPECTRIMS as an appropriate study to include in the indirect treatment comparison (ITC).

North American Study

The North American study (NA study) was a multicentre, phase III randomised clinical trial where 939 patients with SPMS were randomly assigned to receive either IFNβ-1b 250 μg or IFNβ-1b 160 μg or placebo, injected subcutaneously over 3 years. At baseline, mean age, the proportion of females, mean EDSS score, duration of MS and duration of SPMS were

comparable (differences <10%). The patients in the NA study had a higher mean duration of MS than EXPAND (14.7 vs 12.6 years), a lower proportion of these patients were relapse-free in the 2 years prior to the study (55% vs 64%), but they had a higher mean number of relapses per patients in the previous 2 years (0.8 vs 0.7). The remaining baseline characteristics reported in EXPAND study were not reported in the NA Study. The primary outcome was number of days from the start of treatment to the first recorded increase of ≥1.0 point from the baseline EDSS score (≥0.5 point if the baseline EDSS score was 6.0-6.5) confirmed at two consecutives scheduled examinations spanning ≥6 months from the onset of progression. This definition of disease progression is different to the one used in EXPAND. ARR and discontinuation were key secondary outcomes. This is different to the primary endpoint of EXPAND, 3-month CDP. There was no significant difference in time to 6-month CDP between either IFNβ-1b and placebo-treated patients. However, IFNβ-1b treatment showed improvement in the secondary outcome measures. The ERG considers the company's assessment of the NA study appropriate include in the ITC, despite not measuring time to 3-month CDP.

European Study

The European Study (EU study) was a multicentre, phase III randomised clinical trial where 718 patients with SPMS were randomly assigned to receive IFNβ-1b 250 μg or placebo, injected subcutaneously over 3 years. At baseline, the proportion of females, mean EDSS score and duration of MS were comparable to EXPAND (differences <10%). The patients in the European study were younger (41.0 vs 48.0) than patients in EXPAND, a lower proportion of patients had EDSS score ≥6.0 (45% vs 56%), had a shorter mean duration of SPMS (2.2 vs 3.8 years), and a lower proportion of these patients were relapse-free in the 2 years prior to the study (30% vs 64%). The remaining baseline characteristics reported in EXPAND were not reported in the European Study. The primary outcome was Time from baseline to the first scheduled quarterly visit at which an increase by at least 1.0 point of the EDSS (0.5 points if the baseline EDSS was 6.0 or 6.5) was recorded, provided the increase was confirmed at the next scheduled study visit 3 months later (at least 70 days apart). This definition of disease progression is different to the one used in EXPAND. The ARR and discontinuation were key secondary outcomes. Time to 3-month CDP for patients receiving IFNβ-1b was delayed (p=0.007), and the proportion of patients with either progression or relapses decreased by nearly 30% in patients treated with IFNβ-1b

compared with placebo. Statistical analyses were based on the Mantel-Cox log-rank test and Mantel-Haenszel test. The ERG considers this approach to trial statistics appropriate, and the ERG also agree with the company's assessment of the European Study as an appropriate study to include in the ITC.

ASCEND study

ASCEND was a multicentre, phase III randomised clinical trial where 889 patients with SPMS were randomly assigned to receive natalizumab 300 mg or placebo, administered intravenously over 2 years. At baseline, the distributions of age, proportion of females, mean EDSS score, time since onset of MS symptoms, duration of MS, normalised brain volume, total volume of T2 lesions on T2-weighted images, time since most recent relapse, proportion of patients relapse-free in the prior year, and the proportion of patients relapse-free in the prior 2 years in ASCEND were comparable to those in EXPAND. The patients in the ASCEND study had a higher proportion of patients with EDSS score ≥6.0 (63% vs 56%), longer mean duration of SPMS (4.8 vs 3.8 years), higher the proportion of patients with Gd+ lesions of T1-weighted images (24% vs 21%), and a shorted mean timed 25-foot walk test (11.2 vs 16.7 seconds) compared to EXPAND. The remaining baseline characteristics reported in EXPAND study were not reported for ASCEND study. The primary outcome was a multicomponent measure of sustained disability progression over 96 weeks, comprising of increase from baseline by at least 1 EDSS point (or 0.5 point if baseline EDSS was ≥6.0), ≥20% increase in T25FW and ≥20% in 9-HPT. The ARR and discontinuation were key secondary outcomes. The company acknowledges that ACSEND reported time to 96-week CDP only as a composite of multiple scales and is not comparable with the EDSS-specific outcome in EXPAND. Thus, indirect comparisons are instead based on the proportion of patients who experienced 6-months/96-week CDP measured by the EDSS alone. ARR and discontinuation were key secondary outcomes. Natalizumab treatment for SPMS did not reduce progression on the primary multicomponent disability endpoint (OR=0.86; 95% CI: 0.66 to 1.13). Statistical analyses were based on logistic regression, ANCOVA and mixed-effects models, depending on the outcomes. The ERG considers this approach to trial statistics appropriate, and also the ERG agree with the company's assessment of the ASCEND study appropriate to be included in the ITC.

IMPACT study

The ASCEND study was a multicentre, phase III randomised clinical trial where 436 patients with SPMS were randomly assigned to receive interferon β-1a 60 μg or placebo, injected intramuscularly over 2 years. At baseline, age, proportion of females and mean EDSS score were comparable to that in EXPAND. Compared to EXPAND study, the patients in the IMPACT study had a lower proportion of patients with EDSS score ≥6.0 (84% vs. 56%), had a longer mean duration of MS (16.5 vs. 12.6 years), higher proportion of patients with Gd+ lesions of T1-weighted images (36% vs. 21%), a shorter mean timed 25-foot walk test (14.5 vs. 16.7 seconds), shorter time since most recent relapse (44.4 vs. 59.0 months), smaller proportion of patients relapse-free in the prior year (61% vs. 78%), and greater mean number of relapses per patient in the prior year (0.6 vs. 0.2). The remaining baseline characteristics reported in EXPAND were not reported for IMPACT study. The primary outcome was a 2-year change in MS Functional Composite (MSFC) score, comprising of the T25FW, 9-HPT and PASAT. Time to disability progression was defined as an increase of at least 1 EDSS point (or 0.5 point if baseline EDSS was ≥6.0), slightly different to the definition used in EXPAND. The ARR and discontinuation were also key secondary outcomes. There was no significant difference in 3-month CDP based on the EDSS, between patients in the IFNβ-1a and the placebo groups (HR=0.977; 95% CI: 0.679 to 1.407). Statistical analyses were based on the non-parametric ANCOVA, due to the skew of the observed data. The ERG considers this approach to trial statistics appropriate, and agree with the company's assessment of the IMPACT study appropriate to be included in the ITC.

10.1.1 Characteristics of studies included in the ITC

Study	ASCEND[4]	European Study[8, 9]	IMPACT[10]	North American Study[7]	SPECTRIMS[5, 6]
Comparators and dose	Natalizumab (300 mg every 4 weeks, intravenously) vs placebo	Interferon β-1b (0.5 mL for first 2 weeks, increasing to 1.0 mL thereafter, injected subcutaneously every other day) vs placebo	Interferon β-1a (60 µg every week, intramuscular injections) vs placebo	Interferon β-1b (250 µg, injected subcutaneously every other day) vs Interferon β-1b (160 µg, injected subcutaneously every other day) vs placebo	Interferon β-1a (22 µg injected subcutaneously, three times per week) vs Interferon β-1a (44 µg injected subcutaneously, three times per week) vs placebo
Location	163 sites in 17 countries including the UK, the USA, and countries in Europe	32 centres across Europe	42 centres: 31 in the US, 4 in Canada and 7 in Europe	35 centres across the USA and Canada	22 centres across Europe, Canada and Australia
Trial design	1:1, multicentre, phase III randomised clinical trial	1:1, multicentre, phase III randomised clinical trial	Multicentre, phase III randomised clinical trial	1:1:1, multicentre, phase III randomised clinical trial	Multicentre, phase III randomised clinical trial

Eligibility criteria	Aged 18-58 years Onset of SPMS 2 or more years prior to enrolment EDSS score 3.0-6.5 MSSS score of 4 or more Disability progression not related to clinical relapses during the year before enrolment	Aged 18-55 years Clinically or laboratory supported definite diagnosis of MS Secondary progression defined as a period of deterioration independent of relapses, sustained for at least 6 months, and that followed a period of RRMS (superimposed relapses allowed) EDSS score 3.0-6.5 Recorded history of either two relapses or more or 1.0 point or more increase in EDSS in the previous two years	Aged 18-60 years SPMS with or without recent relapse Disease progression over the previous year Cranial MRI demonstrating lesions consistent with MS EDSS score 3.5-6.5	Aged 18-65 years Clinically definite or laboratory-supported definite MS of at least 2 years' duration History of at least one relapse followed by deterioration sustained for at least 6 months EDSS score of at least 3.0-6.5 increase in EDSS score of at least 1.0 point in the 2 years prior to screening or at least 0.5-point increase for subjects with a screening EDSS score of 6.5	Aged 18-55 years Clinically definite SPMS, defined as progressive deterioration of disability for at least 6 months with an increase of at least 1 EDSS point over the last 2 years (or 0.5 point between EDSS score of 6.0 and 6.5), with or without superimposed exacerbations, following an initial RR course EDSS score 3.0-6.5 Pyramidal functional score of at least 2

Outcome of interest	Multicomponent measure of sustained disability progression comprising, 96 week CDP: 1.0/0.5 increase in EDSS 20% or higher increase in T25FW 20% or more increase I n9HPT (either hand)	Time from baseline to the first scheduled quarterly visit at which an increase by at least 1·0 point of the EDSS (0·5 points if the baseline EDSS was 6·0 or 6·5) was recorded, provided the increase was confirmed at the next scheduled study visit 3 months later (at least 70 days apart)	Time to confirmed progression in disability, defined as increase from baseline by at least 1 EDSS point (or 0.5 point if baseline EDSS was ≥ 6.0). MSFC change from baseline to month 24 (mean of the Z-scores of T25FW, 9HPT, PASAT3)	Number of days from the start of treatment to the first recorded increase of ≥1.0 point from the baseline EDSS score (≥0.5 point if the baseline EDSS score was 6.0-6.5) confirmed at two consecutives scheduled examinations spanning ≥6 months from the onset of progression	Time to confirmed progression in disability, defined as increase from baseline by at least 1 EDSS point (or 0.5 point if baseline EDSS was ≥ 5.5), confirmed 3 months later with no intervening score lower than the minimum required level
Crossover details	Optional open-label extension phase where all patients receive natalizumab until the end of the study	NA	NA	NA	NA
Randomisation strata	Site Baseline EDSS score (3.0-5.5 vs 6.0-6.5)	NA	Baseline EDSS score Presence or absence of Gd-enhacing lesions on the baseline MRI	Site	Site

Subgroups	With or without baseline Gd+ lesions and relapses in the 1-2 years before entering the study	Age (< 42 vs >= 42) Sex (male vs female) Baseline EDSS score (<=3.5 vs 4.0-5.5 vs >= 6.0) Duration of MS (<11.9 vs >= 11.9 years) Time since evidence of progressive deterioration and diagnosis of SPMS Number of relapses 2 years before or during the study or both EDSS change in the 2 years before the study (<1 vs =1 vs >1) A combination of the above	Presence or absence of relapses in the year prior to enrolment Baseline EDSS of 3.5-5.5 vs 6.0-6.5 Presence or absence of Gd-enhancing lesions on the baseline MRI scan	NA	Sex (male vs female) Presence or absence of relapses in the 2 years preceding the study

10.2 ERG appendix B

Risk of Bias tables: ERG quality assessment of the EXPAND study and trials included in MAIC

Quality (risk of bias) in EXPAND study included in CS MAIC (as assessed by the company and ERG)[2]

NICE checklist item	CS Appendices Document page 141	ERG judgement	ERG rationale
Was randomisation carried out appropriately?	Low RoB	Low RoB	Kappos 2018 reports interactive response technology for generating the randomisation numbers .
Was the concealment of treatment allocation adequate?	Low RoB	Low RoB	Kappos 2018 reports interactive response technology for concealment of allocation.
Were the groups similar at the outset of the study in terms of prognostic factors?	Low RoB	Low RoB	Kappos 2018 reports that baseline characteristics were similar between groups, shown in Table 1; the CSR reports the baseline demographic characteristics in Table 11-2, page 97, MS disease history in Table 11-3 and other baseline characteristics in Table 11-4 and Table 11-5, and states that they were generally balanced across groups.
Were the care providers, participants and outcome assessors blind to treatment allocation?	Low RoB	Low RoB	Care providers, participants, and outcome assessors blind to treatment allocation (Kappos 2018 describes the trial as double-blind; the CSR, page 29 states that patients, investigator staff, persons performing the assessments, and data analysts remained blinded to the identity of the treatment from the time of randomization until database lock of the Core Part. The identity of the treatments was concealed by the use of study drugs that were identical in packaging, labelling, schedule of administration, appearance, taste, and odour.
Were there any unexpected imbalances in drop-outs between groups?	Low RoB	Low RoB	There were no unexpected imbalances in study withdrawals. The reasons for all withdrawals were explained.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Low RoB	Low RoB	There was no evidence to suggest that the authors measured more outcomes than they reported (all outcomes stated in the methods section were reported).

Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Low RoB	Low RoB	Intention-to-treat analysis, the CSR page 77. The primary analysis of the time to 3-month CDP used all available data from all patients in the FAS, irrespective of premature discontinuation from study medication) and appropriate methods were used to account for missing data (the CSR page 77: Patients who did not reach 3-month CDP during the study were censored at the latest date known to be at risk defined in the FAS as the date of the last EDSS assessment). Sensitivity analyses were also performed on the FAS, using 3 predefined assumptions for determination of confirmed progression.
CDP = Confirmed disability progression; EDSS = Expanded disability status scale; FAS = Full analysis set; ITT = intent to treat; N/A = not applicable; RoB = risk of bias; ERG=evidence review group			

Quality (risk of bias) in ASCEND study included in MAIC (as assessed by the company and ERG)[4]

NICE checklist item	CS Appendices Document page 141	ERG judgement	ERG rationale
Was randomisation carried out appropriately?	Low RoB	Low RoB	Interactive voice/web response system. Patients were stratified by site and by EDSS score (3·0–5·5 vs 6·0–6·5).
Was the concealment of treatment allocation adequate?	Low RoB	Low RoB	Interactive voice/web response system.
Were the groups similar at the outset of the study in terms of prognostic factors?	Low RoB	Low RoB	At baseline for part 1, clinical characteristics were balanced between treatment groups.
Were the care providers, participants and outcome assessors blind to treatment allocation?	Low RoB	Low RoB	Patients and study staff were masked to treatment assignments in part 1 (the randomised, double-blind, parallel-group, placebo-controlled phase). Natalizumab and placebo were of identical appearance. Only the pharmacists preparing the infusion and the pharmacy study monitors were not masked to the study treatment.
Were there any unexpected imbalances in drop-outs between groups?	Low RoB	Low RoB	130/449 (29.0%) discontinued treatment in the placebo group and 103/440 (23.4%) discontinued study drug in the natalizumab group by week 96 (end of the randomised, double-blind, parallel-group, placebo-controlled phase). ITT analysis included 448/449 (99.8%) patients in the placebo group and 439/440 (99.8%) in the natalizumab group.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Low RoB	Low RoB	For the randomised, placebo-controlled phase, the primary outcome was a multicomponent measure of sustained disability progression comprising the EDSS, T25FW and 9HPT. Secondary endpoints included the proportion of patients with consistent improvement in T25FW, change in patient-reported ambulatory status on the MSWS-12, change in patient-reported manual ability based on the ABILHAND questionnaire, patient-reported quality of life with the MSIS-29 physical score, change in whole brain volume between week 24 and week 96, and the proportion of patients with disability progression measured by individual physical EDSS functional system scores. The multicomponent outcome and each component of it were reported. Secondary endpoints were referenced to the appendix for this publication (not seen) but were available from the clinicaltrials.gov record for the study (registration number NCT01416181 given in Kapoor 2018; https://clinicaltrials.gov/ct2/show/results/NCT01416181).

Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Low RoB	Low RoB	All part 1 efficacy analyses were done in the part 1 ITT population, defined as all randomly assigned patients treated at baseline. ITT appropriate; no information on accounting for missing data.

CDP = Confirmed disability progression; EDSS = Expanded disability status scale; FAS = Full analysis set; 9HPT = 9-hole peg test; ITT = intent to treat; N/A = not applicable; MSIS-29 = Multiple Sclerosis Impact Scale-29; MSWS-12 = 12-item Multiple Sclerosis Walking Scale; RoB = risk of bias; T25FW = timed 25-foot walk test.

Quality (risk of bias) in EU study included in MAIC (as assessed by the company and ERG)[8, 9]

NICE checklist item	CS Appendices Document page 141	ERG judgement	ERG rationale
Was randomisation carried out appropriately?	Low RoB	Unclear RoB	Randomisation method not reported.
Was the concealment of treatment allocation adequate?	Low RoB	Low RoB	A central randomisation schedule assigned placebo or interferon β-1b to blocks of six patients in a 1/1 ratio. Access to the code was strictly limited according to study protocol.
Were the groups similar at the outset of the study in terms of prognostic factors?	Low RoB	Low RoB	Treatment groups were comparable for all baseline variables.
Were the care providers, participants and outcome assessors blind to treatment allocation?	Unclear RoB	Low RoB	Interferon β-1b was indistinguishable from placebo. To avoid unmasking as a result of the well-characterised side-effects of interferon β-1b, designated treating physicians were responsible only for general medical care, safety assessments, and treatment of relapses, while designated EDSS physicians did the standardised neurological tests. EDSS physicians received no potentially unmasking information from the treating physicians, and were allowed to speak to patients only as necessary to carry out neurological tests. During EDSS assessments all potential injection sites were covered. Documentation of neurological examinations and functional system and EDSS scores were kept separately by the EDSS physicians.
Were there any unexpected imbalances in drop-outs between groups?	Low RoB	Low RoB	Altogether, 57 patients (31 [8·7%] placebo vs. 26 [7·2%] interferon β-1b) dropped out of the study. There were no significant differences for the reasons given between treatment groups.

Is there any evidence to suggest that the authors measured more outcomes than they reported?	Low RoB	Low RoB	The primary outcome measure was the time from baseline to the first scheduled quarterly visit at which an increase by at least 1·0 point of the EDSS (0·5 points if the baseline EDSS was 6·0 or 6·5) was recorded, provided the increase was confirmed at the next scheduled study visit 3 months later (at least 70 days apart). Further EDSS-related variables included time to becoming wheelchair-bound (i.e., reaching an EDSS score of ≥7·0), the proportion of patients with confirmed progression, proportion of patients becoming wheelchair-bound, and EDSS at the endpoint. Relapse-related variables were ARR, time to first relapse, and proportion of patients with moderate or severe relapses. Other outcomes reported in the methods section were MS-related steroid use and hospital admissions, MRI assessments, neutralising antibodies and safety assessments. All these were reported in the results section.
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Low RoB	Low RoB	All statistical analyses were based on the ITT population, including all data of all patients as randomised. The primary outcome was confirmed by additional ITT analyses counting patients lost to follow-up either as progressed after loss to follow-up or as not progressed by the end of the study.
ARR = annual relapse rate; CDP = Confirmed disability progression; EDSS = Expanded disability status scale; FAS = Full analysis set; ITT = intent to treat; N/A = not applicable; RoB = risk of bias; EU=European			

Quality (risk of bias) in NA study included in MAIC (as assessed by the company and ERG)[7]

NICE checklist item	CS Appendices Document page 142	ERG judgement	ERG rationale
Was randomisation carried out appropriately?	Low RoB	Low RoB	The randomization schedule was generated by the Biostatistics and Data Management Group of Berlex Laboratories (Richmond, CA) using an SAS program (Cary, NC). Randomization allocation was by blocks of six. At the start of the study, each site received an adequate number of blocks, based on assumed patient recruitment, to ensure sequential patient numbering within the site.
Was the concealment of treatment allocation adequate?	Low RoB	Unclear RoB	No information was given about the concealment of the allocation.
Were the groups similar at the outset of the study in terms of prognostic factors?	Low RoB	Low RoB	The three groups were well balanced for baseline demographics, disease characteristics, and MRI variables.
Were the care providers, participants and outcome assessors blind to treatment allocation?	Low RoB	Low RoB	Placebo and treatments were identical in composition, appearance, and volume to the corresponding IFNβ-1b dosing arm (except without active drug). To avoid un-blinding of treatment assignment, separate treating and examining physicians were employed. Treating physicians were responsible for the general medical care of each subject, safety assessments, and treatment of relapses. Examining physicians were responsible for completing standardized neurologic evaluations and were not permitted access to previous examination results or any other information that could potentially un-blind them to treatment assignment. For this reason, injection sites were concealed when subjects were in the presence of the examining physician.
Were there any unexpected imbalances in drop-outs between groups?	Low RoB	Low RoB	Drop-outs from the study were: placebo group: 32/308 (10.4%); IFNβ-1b 250µg: 44/317 (13.9%); IFNβ-1b 160µg: 28/314 (8.9%).

Is there any evidence to suggest that the authors measured more outcomes than they reported?	Low RoB	Low RoB	The primary outcome measure was the number of days from the start of treatment to the first recorded increase of ≥1.0 point from the baseline EDSS score (≥0.5 point if the baseline EDSS score was 6.0 to 6.5) confirmed at two consecutive scheduled examinations spanning ≥6 months from the onset of progression. Secondary and tertiary clinical and MRI outcome measures of efficacy included a variety of relapse-related and MRI-related measures, interventions, social handicap, quality of life, and depression (tabulated): Secondary outcome measures: Mean EDSS change from baseline (average of screen and baseline EDSS subtracted from average of last two EDSS scores) ARR Change in composite neuropsychological test score (Rao Brief Repeatable Battery) from baseline ● PASAT-2 and -3 ● SDMT ● Selective reminding test ● 10/36 spatial recall test ● Word list generation Change in T2-weighted lesion area Active lesion rate (new, recurrent, and newly enlarging or enhancing lesions per year on study) in the monthly scanning cohort only. Tertiary outcomes (referenced to supplementary information): Relapse-related endpoints Interventions for disease-related events Social handicap (Environmental Status Scale) Quality of Life (MSQLI) Depression (Beck Depression Inventory) MRI measures of disease activity (monthly scanning cohort only) The primary outcome of time to EDSS progression was reported in Panitch 2004. All the secondary outcomes listed above were briefly reported in Panitch 2004 and were referenced to supplementary material (available at https://n.neurology.org/content/suppl/2004/10/29/63.10.1788.DC1) The tertiary endpoints briefly reported in Panitch 2004 were time to first relapse, proportion release-free and use of steroids. All tertiary endpoints listed above were referenced to supplementary material (link as above) and all were reported.

Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Low RoB	Low RoB	All statistical analyses were based on the intention-to-treat population, including all data from all subjects as randomized to 3 years or loss to follow-up. All patients are included in all summary tables to the extent of available data. Missing data were not replaced.

ARR = Annual relapse rate; CDP = Confirmed disability progression; EDSS = Expanded disability status scale; FAS = Full analysis set; ITT = intent to treat; MRI = magnetic resonance imaging; MSQLI = Multiple Sclerosis Quality of Life Inventory; N/A = not applicable; PASAT = Paced auditory serial addition test; RoB = risk of bias; SDMT = Symbol digit modalities test.

Quality (risk of bias) in SPECTRIMS study included in MAIC (as assessed by the company and ERG)[5, 6]

NICE checklist item	CS Appendices Document page 142	ERG judgement	ERG rationale
Was randomisation carried out appropriately?	Low RoB	Low RoB	Computer-generated randomisation list
Was the concealment of treatment allocation adequate?	Low RoB	Low RoB	Treatment assignments were provided to investigators in sealed envelopes for emergency use: two envelopes were opened at the request of patients who withdrew due to adverse events.
Were the groups similar at the outset of the study in terms of prognostic factors?	Low RoB	High RoB	For women, the treatment (IFN beta-1a 44 mg) was more effective in reducing the time to disability progression vs. placebo (HR=0.63, 95% CI: 0.45, 0.87). Whereas, this effect was not seen in men (HR=1.30, 95% CI: 0.85, 2.01). The proportion of women was greater in IFN beta-1a 44 mg group vs placebo (67% vs. 60%), which could have exaggerated the effect of IFN beta-1a 44mg relative to placebo.
Were the care providers, participants and outcome assessors blind to treatment allocation?	Low RoB	Low RoB	Solutions of IFNβ-1a and placebo were physically indistinguishable, and packaging and labelling were prepared to preserve blinding. The manufacturer labelled containers of study medication with patient identification numbers based on the randomisation list, and patients received the medication labelled with their numbers. Because IFN side effects are well recognised, a treating physician supervised drug administration, monitored safety, and managed adverse events, and a separate evaluating physician conducted neurologic assessments and followed up exacerbations. Patients were instructed to cover injection sites and to discuss only neurologic matters during neurologic examinations. Clinical and neurologic data were recorded in separate binders.
Were there any unexpected imbalances in drop-outs between groups?	Low RoB	Low RoB	Drop-outs: 19/205 (9.3%) in placebo group; 14/209 (6.7%) in Rebif 22 mcg group; 14/204 (6.9%) in Rebif 44 mcg group.

Is there any evidence to suggest that the authors measured more outcomes than they reported?	Low RoB	Low RoB	The primary efficacy outcome was time to confirmed progression in disability. Secondary outcomes included proportion of patients progressing; exacerbation count; time to first exacerbation; time between first and second exacerbations; number of moderate and severe exacerbations; number of steroid courses and hospitalisations for MS; IDSS; composite score (rank values for time to progression, exacerbation rate, MRI lesion burden, MRI T2 activity and IDSS). All were reported in the results except the IDSS and MRI outcomes were not reported separately, only in the composite score.
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Low RoB	Low RoB	ITT; patients who dropped out were considered censored; no imputation was used.
CDP = Confirmed disability progression; EDSS = Expanded disability status scale; FAS = Full analysis set; IDSS = integrated disability status score (area under an EDSS time curve, adjusted for baseline); ITT = intent to treat; N/A = not applicable; RoB = risk of bias; HR=hazard rate ratio			

Quality (risk of bias) in IMPACT study included in MAIC (as assessed by the company and ERG)[10]

NICE checklist item	CS Appendices Document page 142	ERG judgement	ERG rationale
Was randomisation carried out appropriately?	Low RoB	Unclear RoB	Randomisation method not described
Was the concealment of treatment allocation adequate?	Low RoB	Unclear RoB	No information on allocation concealment
Were the groups similar at the outset of the study in terms of prognostic factors?	Low RoB	Low RoB	Demographic, clinical, and MRI features of the two treatment groups were well matched at baseline
Were the care providers, participants and outcome assessors blind to treatment allocation?	Unclear RoB	Unclear RoB	Care providers/participants Not stated Outcome assessors Each study site designated a treating nurse, treating neurologist, examining technician, and examining neurologist. The treating nurse and neurologist were responsible for clinical management of the subjects. The examining technician administered the MSFC, and the examining neurologist determined the EDSS during all scheduled study visits. Neither the examining technician nor the examining neurologist was involved with any other aspect of subject care, and neither had access to the results of prior examinations or to clinical information that might compromise blinding.
Were there any unexpected imbalances in drop-outs between groups?	Low RoB	Low RoB	23/219 (11%) subjects in the placebo group vs. 29/217 (13%) subjects in the IFNβ-1a group failed to complete 24 months of follow-up.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Low RoB	Low RoB	The primary outcome measure was the MSFC (the mean of the Z-scores of the T25FW, 9HPT, and PASAT3) change from baseline to month 24. EDSS progression, relapse rate, MRI, and HRQOL were also stated in the methods section as being assessed. All these outcomes were reported in Cohen 2002 or in the supplementary material at https://n.neurology.org/content/suppl/2002/08/26/59.5.679.DC1
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Low RoB	Low RoB	All randomized subjects served as the intent-to-treat evaluation cohort with missing data points imputed using the last available observation carried forward.

CDP = Confirmed disability progression; EDSS = Expanded disability status scale; FAS = Full analysis set; Gd = gadolinium; 9HPT = 9-hole peg test; ITT = intent to treat; MRI = magnetic resonance imaging; MDFC = multiple sclerosis functional composite; N/A = not applicable; PASAT = Paced auditory serial addition test; RoB = risk of bias; T25FW = timed 25-foot walk test.

10.3 ERG appendix C

Effect modifiers

As discussed in the ERG main report, the ERG considered the CS process used to identify EM lacked transparency. Therefore, we conducted visual inspections of the univariate analysis of the effect modifiers (CS Appendix section D.1.5. Figure 3 and Figure 4) across all six trials included in the SLR. The ERG comparisons for three key outcomes (10.3.1, 10.3.2, 10.3.3) are provided in Table 78 to Table 87 (6-month CDP is presented in the ERG main report).

10.3.1 Proportion 6-month CDP

Table 78. Comparison of EM ASCEND vs. EXPAND

Effect modifiers	**ASCEND[4] Natalizumab**	**EXPAND**		
		Overall	**Matched**	**Unmatched**
N	887	[redacted]	[redacted]	[redacted]
Age	47.25 (7.61)	[redacted]	[redacted]	[redacted]
EDSS score at screening	5.6 (0.9)	[redacted]	[redacted]	[redacted]
MS duration since diagnosis	12.14 (6.88)	[redacted]	[redacted]	[redacted]
Prior DMT	77.00%	[redacted]	[redacted]	[redacted]
Normalised Brian Volume	1423.37 (82.95)	[redacted]	[redacted]	[redacted]
Patients with Gd-enhacing T1 lesions	76.20%	[redacted]	[redacted]	[redacted]
Duration of SPMS	4.8 (3.37)	[redacted]	[redacted]	[redacted]
Total volume of T2 lesions	16793.21 (17003.8)	[redacted]	[redacted]	[redacted]
Relapse free in prior 2 years	70.70%	[redacted]	[redacted]	[redacted]
Sex (female)	62.00%	[redacted]	[redacted]	[redacted]
Outcome measure				

Proportion with 6-month CDP				
HR (95% CI)	1.06 (0.74, 1.53)	[redacted]	Not reported	Not reported
P-value			Not reported	Not reported
Not reported for proportion wit 6-month CDP				
Effect modifiers	**Subgroup**	**Siponimod, N (%)**	**Placebo, N (%)**	**HR (95% CI)**
Overall	**Overall**			
Age	< 42			
	>= 42			

10.3.2 3-month CDP

Table 79. Comparison of EM SPECTRIMS (22) vs. EXPAND

Effect modifiers	**SPECTRIMS Interferon b-1a 22**	**EXPAND**		
		Overall	**Matched**	**Unmatched**
N	618	[redacted]	[redacted]	[redacted]
Age	42.8 (7.1)	[redacted]	[redacted]	[redacted]
EDSS score at screening	5.4 (1.1)	[redacted]	[redacted]	[redacted]
MS duration since diagnosis	13.3 (7.1)	[redacted]	[redacted]	[redacted]
Duration of SPMS	4 (3)	[redacted]	[redacted]	[redacted]
Number of relapses in prior 2 years	0.9 (1.3)	[redacted]	[redacted]	[redacted]
Sex (female)	63.00%	[redacted]	[redacted]	[redacted]
Outcome measure				
Time to 3-month CDP				
Intervention	Not reported	288/1096 (26.3%)	Not reported	Not reported
Placebo	Not reported	173/345 (31.7%)	Not reported	Not reported
HR (95% CI)	0.88 (0.69, 1.12)*	0.79 (0.65, 0.95)	Not reported	Not reported
P-value	Not reported	0.0134	Not reported	Not reported

*HR/CI not reported so was estimated

Effect modifiers	**Subgroup**	**Siponimod, N (%)**	**Placebo, N (%)**	**HR (95% CI)**
Overall	**Overall**	**1099**	**546**	**0.78 (0.65, 0.94)**
Age	< 42	218	113	0.70 (0.48, 1.03)
	>= 42	878	432	0.80 (0.65, 1.00)
EDSS score at screening	3.0-5.5	474	248	0.68 (0.52, 0.88)

	6.0-6.5	614	294	0.88 (0.67, 1.16)
MS duration since diagnosis	<11.9	541	288	0.73 (0.56, 0.93)
	>=11.9	553	257	0.87 (0.65, 1.16)
Duration of SPMS	<1.3	256	148	0.73 (0.51, 1.05)
	>=1.3	838	397	0.80 (0.64, 1.00)
Number of relapses in prior 2 years	1	198	104	0.62 (0.41, 0.94)
	2	107	57	0.83 (0.49, 1.49)
	>2	83	41	0.59 (0.29, 1.21)
Sex	Female	826	414	0.82 (0.66, 1.02)
	Male	235	114	0.65 (0.43, 0.97)

Table 80. Comparison of EM SPECTRIMS (44) vs. EXPAND

Effect modifiers	**SPECTRIMS Interferon b-1a 22**	**EXPAND**		
		Overall	**Matched**	**Unmatched**
N	618	[redacted]	[redacted]	[redacted]
Age	42.8 (7.1)	[redacted]	[redacted]	[redacted]
EDSS score at screening	5.4 (1.1)	[redacted]	[redacted]	[redacted]
MS duration since diagnosis	13.3 (7.1)	[redacted]	[redacted]	[redacted]
Duration of SPMS	4 (3)	[redacted]	[redacted]	[redacted]
Number of relapses in prior 2 years	0.9 (1.3)	[redacted]	[redacted]	[redacted]
Sex (female)	63.00%	[redacted]	[redacted]	[redacted]
Outcome measure				
Time to 3-month CDP				
Intervention	Not reported	288/1096 (26.3%)	Not reported	Not reported
Placebo	Not reported	173/345 (31.7%)	Not reported	Not reported
HR (95% CI)	0.83 (0.65, 1.07)	0.79 (0.65, 0.95)	Not reported	Not reported
P-value	0.146	0.0134	Not reported	Not reported

Effect modifiers	**Subgroup**	**Siponimod, N (%)**	**Placebo, N (%)**	**HR (95% CI)**
Overall	**Overall**	**1099**	**546**	**0.78 (0.65, 0.94)**
Age	< 42	218	113	0.70 (0.48, 1.03)
	>= 42	878	432	0.80 (0.65, 1.00)
EDSS score at screening	3.0-5.5	474	248	0.68 (0.52, 0.88)
	6.0-6.5	614	294	0.88 (0.67, 1.16)
MS duration since diagnosis	<11.9	541	288	0.73 (0.56, 0.93)
	>=11.9	553	257	0.87 (0.65, 1.16)

Duration of SPMS	<1.3	256	148	0.73 (0.51, 1.05)
	>=1.3	838	397	0.80 (0.64, 1.00)
Number of relapses in prior 2 years	1	198	104	0.62 (0.41, 0.94)
	2	107	57	0.83 (0.49, 1.49)
	>2	83	41	0.59 (0.29, 1.21)
Sex	Female	826	414	0.82 (0.66, 1.02)
	Male	235	114	0.65 (0.43, 0.97)

Table 81. Comparison of EM EU study vs. EXPAND

Effect modifiers	**EU Study Interferon b 1b**	**EXPAND**		
		Overall	**Matched**	**Unmatched**
N	718	[redacted]	[redacted]	[redacted]
Age	41 (7.2)	[redacted]	[redacted]	[redacted]
EDSS score at screening	5.15 (1.1)	[redacted]	[redacted]	[redacted]
MS duration since diagnosis	13.1 (7.06)	[redacted]	[redacted]	[redacted]
Duration of SPMS	2.15 (2.3)	[redacted]	[redacted]	[redacted]
Relapse-free in prior 2 years	30.40%	[redacted]	[redacted]	[redacted]
Sex (female)	61.10%	[redacted]	[redacted]	[redacted]
Outcome measure				
Time to 3-month CDP				
Intervention		288/1096 (26.3%)	Not reported	Not reported
Placebo		173/345 (31.7%)	Not reported	Not reported
HR (95% CI)	0.74 (0.60, 0.91)*	0.79 (0.65, 0.95)	Not reported	Not reported
P-value		0.0134	Not reported	Not reported

*HR/CI not reported so was estimated

Effect modifiers	**Subgroup**	**Siponimod, N (%)**	**Placebo, N (%)**	**HR (95% CI)**
Overall	**Overall**	**1099**	**546**	**0.78 (0.65, 0.94)**
Age	< 42	218	113	0.70 (0.48, 1.03)
	>= 42	878	432	0.80 (0.65, 1.00)
EDSS score at screening	3.0-5.5	474	248	0.68 (0.52, 0.88)
	6.0-6.5	614	294	0.88 (0.67, 1.16)
MS duration since diagnosis	<11.9	541	288	0.73 (0.56, 0.93)

	>=11.9	553	257	0.87 (0.65, 1.16)
Duration of SPMS	<1.3	256	148	0.73 (0.51, 1.05)
	>=1.3	838	397	0.80 (0.64, 1.00)
Relapse free in prior 2 years	No	388	202	0.67 (0.49, 0.91)
	Yes	708	343	0.86 (0.67, 1.09)
Sex	Female	826	414	0.82 (0.66, 1.02)
	Male	235	114	0.65 (0.43, 0.97)

Table 82. Comparison of EM IMPACT study vs. EXPAND

Effect modifiers	IMPACT Interferon b 1a	EXPAND		
		Overall	Matched	Unmatched
N	436	[redacted]	[redacted]	[redacted]
Age	47.55 (7.95)	[redacted]	[redacted]	[redacted]
EDSS score at screening	5.2 (1.1)	[redacted]	[redacted]	[redacted]
MS duration since diagnosis	16.45 (9)	[redacted]	[redacted]	[redacted]
1 Gd- enhancing T1 lesion	16.50%	[redacted]	[redacted]	[redacted]
2 Gd- enhancing T1 lesions	5.80%	[redacted]	[redacted]	[redacted]
3 Gd- enhancing T1 lesions	3.60%	[redacted]	[redacted]	[redacted]
4 Gd-enhancing T1 lesions	10.30%	[redacted]	[redacted]	[redacted]
Number of relapses in prior 1 year	0.55 (1)	[redacted]	[redacted]	[redacted]
Sex (female)	64.00%	[redacted]	[redacted]	[redacted]
Outcome measure				
Time to 3-month CDP				
Intervention		288/1096 (26.3%)	Not reported	Not reported
Placebo		173/345 (31.7%)	Not reported	Not reported
HR (95% CI)	0.977 (0.68, 1.41)	0.79 (0.65, 0.95)	Not reported	Not reported
P-value	0.9	0.0134	Not reported	Not reported

Effect modifiers	Subgroup	Siponimod, N (%)	Placebo, N (%)	HR (95% CI)
Overall	**Overall**	**1099**	**546**	**0.78 (0.65, 0.94)**
Age	< 42	218	113	0.70 (0.48, 1.03)
	>= 42	878	432	0.80 (0.65, 1.00)
EDSS score at screening	3.0-5.5	474	248	0.68 (0.52, 0.88)
	6.0-6.5	614	294	0.88 (0.67, 1.16)

MS duration since diagnosis	<11.9	541	288	0.73 (0.56, 0.93)
	>=11.9	553	257	0.87 (0.65, 1.16)
Number of relapses in prior 1 year	No	187	111	0.63 (0.41, 0.97)
	Yes	37	18	0.93 (0.30, 2.90)
Sex	Female	826	414	0.82 (0.66, 1.02)
	Male	235	114	0.65 (0.43, 0.97)

10.3.3 ARR

The ERG note that univariate regression for ARR was not presented in the CS Appendix section D.1.5.

Table 83. Comparison of EM SPECTRIMS 22 vs. EXPAND

Effect modifiers	**SPECTRIMS Interferon b-1a 22**	**EXPAND**		
		Overall	**Matched**	**Unmatched**
N	616	[redacted]	[redacted]	
Mean number of relapses in prior 2 years	0.9 (1.3)	[redacted]	[redacted]	
Outcome measure				
ARR				
Intervention		0.071 (0.055, 0.092)		
Placebo		0.160 (0.12, 0.207)		
HR (95% CI)	0.69 (0.56, 0.84)	0.45 (0.34, 0.59)		
P-value		< 0.0001		

Table 84. Comparison of EM SPECTRIMS 44 vs. EXPAND

Effect modifiers	**SPECTRIMS Interferon b-1a 44**	**EXPAND**		
		Overall	**Matched**	**Unmatched**
N	616	[redacted]	[redacted]	
Mean number of relapses in prior 2 years	0.9 (1.3)	[redacted]	[redacted]	
Outcome measure				
ARR				
Intervention		0.071 (0.055, 0.092)		
Placebo		0.160 (0.12, 0.207)		
HR (95% CI)	0.69 (0.56, 0.85)	0.45 (0.34, 0.59)		
P-value		< 0.0001		

Table 85. Comparison of EM NA and EU study vs. EXPAND

Effect modifiers	**NA + Eu Study Interferon b-1b**	**EXPAND**		
		Overall	**Matched**	**Unmatched**
N	1343	[redacted]	[redacted]	
NONE				
Outcome measure				
ARR				
Intervention		0.071 (0.055, 0.092)		
Placebo		0.160 (0.12, 0.207)		
HR (95% CI)	0.65 (0.48, 0.88)	0.45 (0.34, 0.59)		
P-value		< 0.0001		

Table 86. Comparison of EM ASCEND vs. EXPAND

Effect modifiers	**ASCEND Natalizumab**	**EXPAND**		
		Overall	**Matched**	**Unmatched**
N	[redacted]	[redacted]	[redacted]	-
Mean years since most recent relapse	[redacted]	[redacted]	[redacted]	-
Proportion of patients with no Gd+ lesiosn on T1-weighted images	[redacted]	[redacted]	[redacted]	-
Mean total volume of lesions on T2-weighted images	[redacted]	[redacted]	[redacted]	-
Outcome measure				
ARR				
Intervention		0.071 (0.055, 0.092)		
Placebo		0.160 (0.12, 0.207)		
HR (95% CI)	0.453 (0.32, 0.63)	0.45 (0.34, 0.59)		
P-value		< 0.0001		

Table 87. Comparison of EM IMPACT vs. EXPAND

Effect modifiers	**IMPACT Interferon b-1a**	**EXPAND**		
		Overall	**Matched**	**Unmatched**
N	436	[redacted]	[redacted]	-
Mean years since most recent relapse	3.7 (5.1)	[redacted]	[redacted]	-
Number of relapses in prior 1 year	0.55 (1)	[redacted]	[redacted]	-
1 Gd+ lesions on T1-weighted image	16.50%	[redacted]	[redacted]	-
2 Gd+ lesions on T1-weighted image	5.80%	[redacted]	[redacted]	-
3 Gd+ lesions on T1-weighted image	3.60%	[redacted]	[redacted]	-
>=4 Gd+ lesions on T1-weighted image	10.30%	[redacted]	[redacted]	-
Outcome measure				
ARR				
Intervention	0.2	0.071 (0.055, 0.092)		
Placebo	0.3	0.160 (0.12, 0.207)		
HR (95% CI)	0.67 (0.49, 0.90)	0.45 (0.34, 0.59)		
P-value	0.008	< 0.0001		

10.4 ERG NMA results

As discussed in the main ERG report, the ERG conducted exploratory NMA of all outcomes included in the CS MAIC. Results for 6-month CDP and ARR are presented in the ERG report, results for 3-month CDP and proportion with 6-months (96w) CDP are provided in Table 88 to Table 91 and the network of intervention diagrams are presented in Figure 15 and Figure 16.

10.4.1 Time to 3-month CDP NMA results

Table 88. Data used by the ERG in the NMA

Study	Treatment 1	Treatment 2	Hazard ratio	95% CI	
EXPAND[2]	Siponimod	Placebo	0.79	0.65	0.95
SPECTRIMS[5, 6]	Interferon- β-1a 22 (µg)	Placebo	0.88	0.69	1.12
	Interferon- β-1a 44 (µg)	Placebo	0.83	0.65	1.07
EU study[8, 9]	Interferon- β-1b	Placebo	0.74	0.60	0.91
IMPACT[10]	Interferon- β-1a 60 (µg)	Placebo	0.977	0.68	1.41

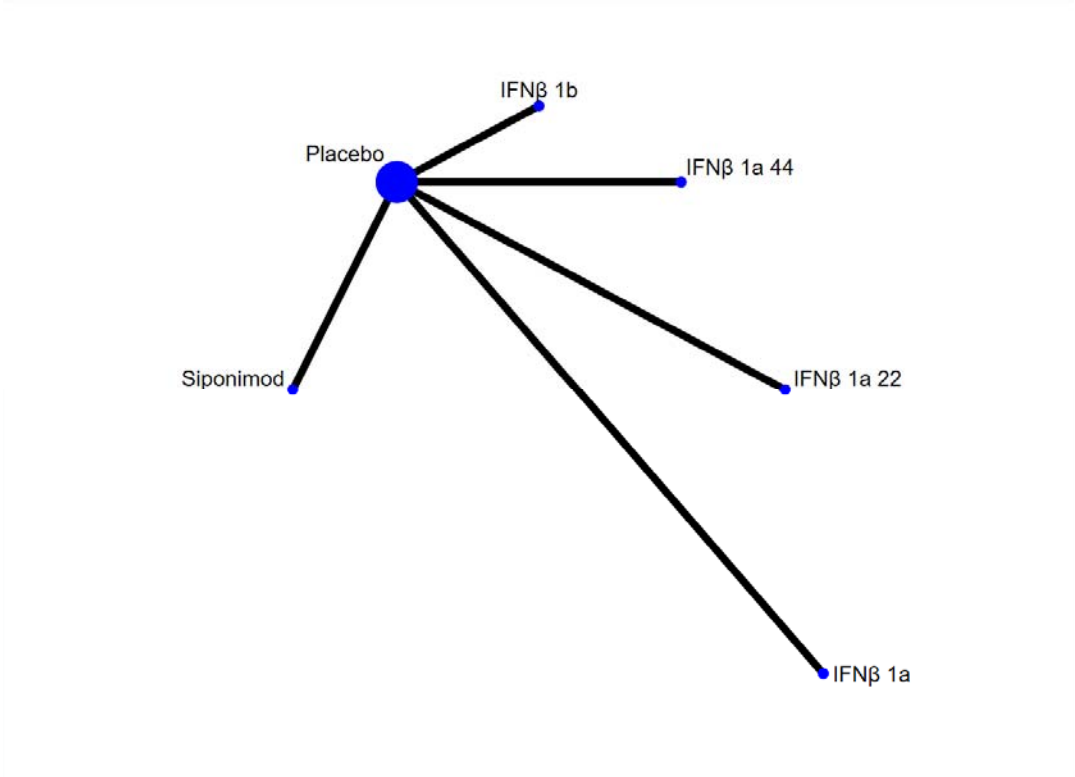


Figure 15.ERG network diagram: 3-month CDP

Table 89. 3-month CDP estimates for ITC of siponimod vs. comparator: CS MAIC vs. ERG NMA

			Siponimod vs. Comparator	
Comparator	**Regimen**	**Study ID**	**Company MAIC**	**ERG NMA**
SC IFNβ-1a	22 µg TIW	SPECTRIMS	[redacted]	0.90 (0.66, 1.22)
	44 µg TIW	SPECTRIMS	[redacted]	0.79 (0.66, 0.95)
SC IFNβ-1b	250 µg Q2D	European Study	[redacted]	1.07 (0.81, 1.41)
IM IFNβ-1a	60 µg QW	IMPACT	[redacted]	0.81 (0.54, 1.22)

10.4.2 Proportion with 6-months (96w) CDP NMA

Table 90. Data used by the ERG in the NMA

Study	Treatment 1	Treatment 2	Estimate	95% CI	
EXPAND[2]	Siponimod	Placebo	[redacted]	[redacted]	[redacted]
ASCEND[4]	Natalizumab	Placebo	OR 1.06	0.74	1.53

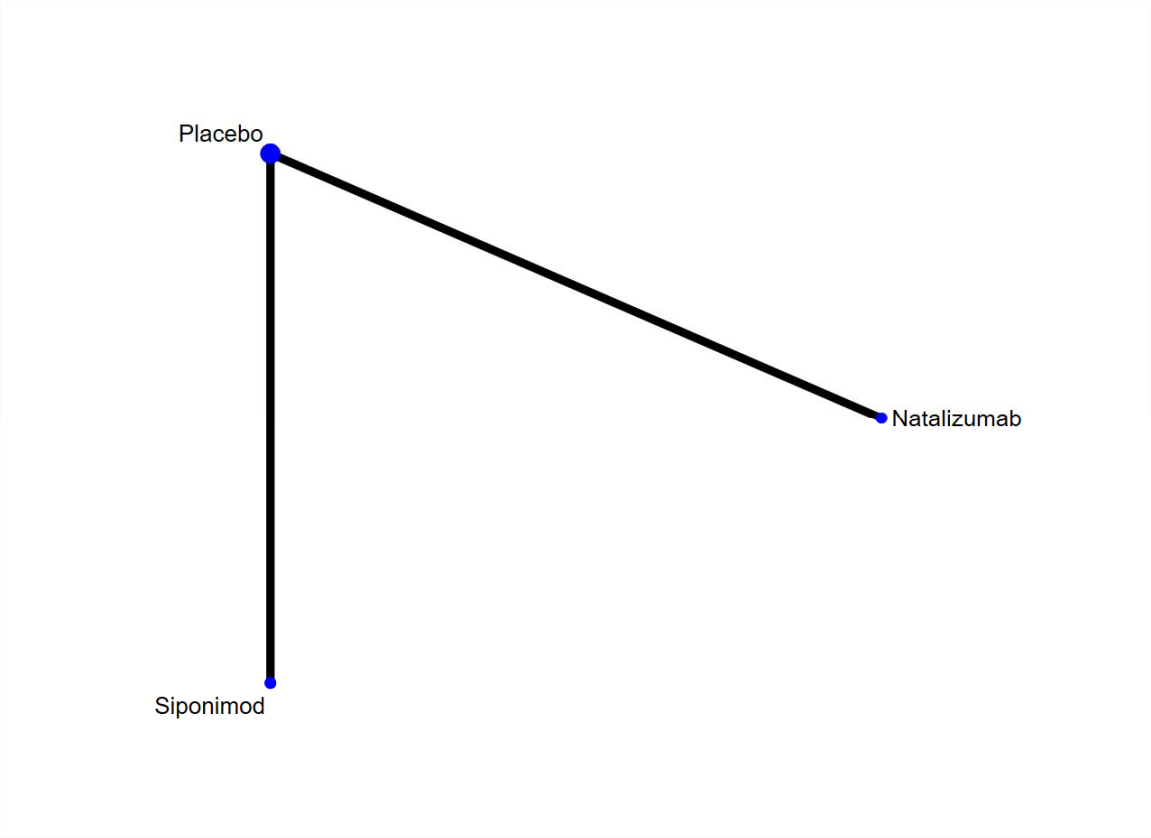


Figure 16. ERG network diagram: proportion with 6-month CDP

Table 91. Proportion with 6-month CDP estimates for ITC of siponimod vs. comparator: CS MAIC vs ERG NMA

			Siponimod vs. Comparator	
Comparator	**Regimen**	**Study ID**	**Company MAIC**	**ERG NMA**
Natalizumab	300 mg Q4W	ASCEND	[redacted]	0.73 (0.47-1.12)

10.5 Appendix D

ERG's individual parameter changes to the Company's base-case analysis.

Table 92. Summary of ERG changes made in the economic model in order to implement the ERG preferred base case

Description of ERG change to economic model	Implementation of the change in the model
Company's base-case model	
Source of disability progression and relapse effectiveness from the ERG's NMA	Settings worksheet, source of disability progression effectiveness, select 'non-MAIC' from the drop-down' menu. Settings worksheet, source of relapse effectiveness, select 'non-MAIC' from the drop-down menu.
Source of natural history, London Ontario database[11]	Settings worksheet, source of NH disability progression, select London Ontario database from the drop-down menu.
Exponential parametric curve fitted to discontinuation data (and time constant discontinuation rates)	Settings worksheet, treatment discontinuation type, select Time constant discontinuation rates from the drop-down menu. Settings worksheet, select distribution for siponimod discontinuation, select Exponential from the drop-down menu.
Treatment effect applied as a rate	Transition Probability worksheet, cell G56 select Apply as rate from drop-down menu.
Health state utility values from Orme et al. (2007)(Orme et al., 2007)	Settings worksheet, source of health state utilities, select Orme et al. (2007) from the drop-down menu.
Cost of £35 for genotyping borne by the company	Settings worksheet, costs for genotyping borne by company, select Yes from the drop-down menu.
Health state management costs obtained from TA320[18]	Inputs Repository, cells D304-D313 change inputs to those reported in TA320, cells E304 change formula to D304*($G$268/$G$262) and copy to E314. These uprated costs should be automatically updated in the Costs worksheet cells E57 to O57.
Additional deterministic analyses (Table 3X)	
Source of natural history, EXPAND and London Ontario database[11] (TPs obtained from the ICER report[35])	NH-Disability Progression worksheet, under the NH transitions based on London Ontario database change cells E29:O39 to reflect the values reported in the ICER report.
Source of natural history, London Ontario[11] (TPs obtained from the ICER report[35])	NH-Disability Progression worksheet, under the NH transitions based on London Ontario database change cells E29:O39 to reflect the values reported in the ICER report. Settings worksheet, source of NH disability progression (cell D47), select 'London Ontario database' from the drop-down menu
Additional deterministic analyses comparing siponimod versus best supportive care	
Siponimod versus BSC (non-MAIC), natural history disability progression from EXPAND and London Ontario database[11]	Settings worksheet, select 'non-MAIC' for both source of disability progression effectiveness and source of relapse effectiveness. Also, under the treatment selection, non-MAIC comparator select BSC from the drop-down menu.
Siponimod versus BSC (non-MAIC), natural history disability progression from	Settings worksheet, select 'non-MAIC' for both source of disability progression effectiveness and source of relapse effectiveness.

London Ontario database[11] derived by the company	Under the treatment selection, non-MAIC comparator select BSC from the drop-down menu. Under the natural history settings, source of NH disability progression, select 'London Ontario database' from the drop-down menu.
Siponimod versus BSC (non-MAIC), natural history disability progression from London Ontario database[11] as presented in the ICER report[35]	Settings worksheet, select 'non-MAIC' for both source of disability progression effectiveness and source of relapse effectiveness. Under the treatment selection, non-MAIC comparator select BSC from the drop-down menu. Under the natural history settings, source of NH disability progression, select 'London Ontario database' from the drop-down menu. NH-Disability Progression worksheet, under the NH transitions based on London Ontario database change cells E29:O39 to reflect the values reported in the ICER report.
Siponimod versus BSC (non-MAIC), natural history, EXPAND and London Ontario database[11] (TPs obtained from the ICER report[35])	Settings worksheet, select 'non-MAIC' for both source of disability progression effectiveness and source of relapse effectiveness. Under the treatment selection, non-MAIC comparator select BSC from the drop-down menu. Under the natural history settings, source of NH disability progression, select 'EXPAND and London Ontario database' from the drop-down menu. NH-Disability Progression worksheet, under the NH transitions based on London Ontario database change cells E29:O39 to reflect the values reported in the ICER report.
ERG's base-case and scenario analysis	
ERG's base-case	Settings worksheet, source of disability progression effectiveness, select 'non-MAIC' from the drop-down' menu. Settings worksheet, source of relapse effectiveness, select 'non-MAIC' from the drop-down menu. Settings worksheet, source of NH disability progression, select London Ontario database from the drop-down menu. Settings worksheet, treatment discontinuation type, select Time constant discontinuation rates from the drop-down menu. Settings worksheet, select distribution for siponimod discontinuation, select Exponential from the drop-down menu. Transition Probability worksheet, cell G56 select Apply as rate from drop-down menu. Settings worksheet, source of health state utilities, select Orme et al. (2007) from the drop-down menu. Settings worksheet, costs for genotyping borne by company, select Yes from the drop-down menu. Inputs Repository, cells D304-D313 change inputs to those reported in TA320, cells E304 change formula to D304*($G$268/$G$262) and copy to E314. These uprated costs should be automatically updated in the Costs worksheet cells E57 to O57.
Source of disability progression and relapse effectiveness from the ERG's NMA	Settings worksheet, source of disability progression effectiveness, select 'MAIC' from the drop-down' menu. Settings worksheet, source of relapse effectiveness, select 'MAIC' from the drop-down menu.

Adverse treatment costs (£4,357) obtained from TA527	Settings worksheet, source of relapse costs, select 'TA527 – RSS model' from the drop-down menu.
Natural history disability progression from London Ontario database[11] derived by the company	Settings worksheet, source of disability progression, select 'EXPAND and London Ontario database' from the drop-down menu.
Source of caregiver disutility obtained from Acaster et al. (Acaster et al., 2013)	Settings worksheet, source of caregiver disutility, select 'Acaster et al. (2013)' from the drop-down menu.
Natural history annualised relapse rates derived from Patzold and Pocklington (1982)[75] and UK MS Survey[12]	Settings worksheet, NH- relapse (ARR) approach, select EDSS (Patzold et al. (1982) + UK MS survey)

ARR, annualised relapse rates, EDSS, expanded disability status scale; ERG, evidence review group; MAIC, matched-adjusting indirect comparison; NH, natural history; NMA, network meta-analysis, SPMS, secondary progressive multiple sclerosis; TA, technology appraisal; TP, transition probability

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

ERG report – factual accuracy check

Siponimod for treating secondary progressive multiple sclerosis [ID1304]

You are asked to check the ERG report to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies, you must inform NICE by **12noon on Friday 22 November 2019** using the below comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

The factual accuracy check form should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Factually Inaccurate Statements

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 15 and 45 of the ERG Report states that *"The primary endpoint of EXPAND was the percentage of participants with 3-month CDP events."* Please accept our apologies for incorrectly stating the primary endpoint of EXPAND in CS Document B, Table 3, Page 23. The primary endpoint is as stated in all other instances in CS Document B: *"The primary endpoint of EXPAND was time to 3-month CDP."*	This statement on page 15 and 45 should be amended to: *"The primary endpoint of EXPAND was time to 3-month CDP."*	The current statement incorrectly describes the primary endpoint of the pivotal EXPAND trial.	The ERG will amend accordingly and note the error in the CS Document B, Table 3, Page 23. *"The primary endpoint of EXPAND was time to 3-month CDP."*

Page 16 of the ERG Report states: *"The comparator trials included in the MAIC analyses generally had similar inclusion/exclusion criteria."* However, this conflicts with the following statement from the ERG on Page 81: *"The reduction of such magnitude in the sample size suggests substantial heterogeneity in the inclusion/exclusion criteria of SPMS patients across the EXPAND study and the other five trials included in the MAIC."*	The statement on page 16 should be removed, as it conflicts with the ERG's conclusions later in the report, and also with the information presented in CS Document B.2.9.2 to support the substantial heterogeneity of the trials included in the MAIC.	The current statement on page 16 is inaccurate and conflicts with the ERG's conclusions later in the report.	The ERG understands the comment and appreciates the confusion. We will amend the first sentence on page 16 to the following: *"The comparator trials included in the MAIC analyses generally had similar inclusion/exclusion criteria. However, there were specific differences in the inclusion and exclusion of patients with SPMS in the EXPAND trial and the other five trials"*
Page 16 of the ERG Report notes rationale for why the CS MAIC should be interpreted with caution. The following statement is incorrect: *"Cross-trial heterogeneity in populations characteristics, and limited relevance of the comparator treatment trials' populations (e.g., RRMS)"* All trials included in the CS MAIC were for patients with SPMS. Therefore, the reference to RRMS trial populations is incorrect.	The reference to RRMS trial populations on page 15 should be removed, and the statement amended to the following: *"Cross-trial heterogeneity in populations characteristics"*	The current statement incorrectly describes the patient populations of the trials included in the CS MAIC.	The ERG agree this is an error, we will amend the sentence to state: *"Cross-trial heterogeneity in populations characteristics, and limited relevance of the comparator treatment trials' populations"*

Page 18 of the ERG Report states: *"The ERG note that participants were excluded without explanation from the unmatched and unadjusted EXPAND population in the MAIC:"* Please note, this exclusion of patients only applies to the MAIC scenario tables (unmatched and unadjusted column), in order to be transparent on the available IPD for the adjusting variables.	This statement should be amended as follows: *"Patients with missing variables had to be excluded prior to the matching and adjusting process in line with the requirements of MAIC methodology. The ERG note that the number of these exclusions was small and transparently presented."*	The current statement does not acknowledge that the excluded participants represent a small number, applicable only to the scenario tables.	The ERG will amend the sentence to state: *".. EXPAND population in the MAIC scenario tables"*
Page 21 of the ERG Report states: *"The treatment effect for siponimod compared to interferon β-1b was applied as a rate as opposed to a probability."* This is incorrect. Novartis can confirm that the treatment effect for siponimod compared to interferon β-1b was applied as a *probability*, not a rate. Page 23 correctly states that applying the treatment effect for siponimod compared to interferon β-1b as a rate as opposed to a probability was an exploratory analysis performed by the ERG, therefore representing a change from the company cost-effectiveness model.	The statement on page 21 should be removed.	The current statement is incorrect. The factually correct statement would be as follows, and would no longer represent a concern for the ERG: *"The treatment effect for siponimod compared to interferon β-1b was applied as a probability, not a rate."*	The ERG agree that this is a factual inaccuracy, and should be changed to the following *"the treatment effect for siponimod compared to interferon β-1b was applied as a probability as opposed to a rate"*. The ERG have explored this as an exploratory analysis, which formed the basis of the ERG's preferred assumptions.

Page 22 of the ERG Report states: *"In general, the results in the CS Document B were in good agreement with those reported in the company's economic model. However, there were instances in the base-case where the model inputs were not consistent to those in the economic model."* Novartis is aware of the one discrepancy in the source of relapse costs quoted in CS Document B vs the economic model. However, we did not see other discrepancies noted in the ERG report.	If the ERG note no further discrepancies between the model inputs in CS Document B vs the economic model (beyond the relapse cost), please amend sentence to: *"In general, the results in the CS Document B were in good agreement with those reported in the company's economic model. However, there was one instance in the base-case of a model input not being consistent to that in the economic model."* If you are aware of further discrepancies, please could the ERG describe these.	Novartis is aware of only one instance of an inconsistency between CS Document B and the economic model.	As stated in the ERG report, we identified the following inconsistencies: First, Figure 15 on Page 105 reports the Weibull parametric fit to the discontinuation data. To our knowledge, this is the exponential fit to the discontinuation data. Second, the probability of siponimod being cost-effective at a willingness-to-pay threshold of £30,000 per QALY. Table 75 on page 122 stated [redacted], but the economic model suggested [redacted]. CS document B states a [redacted] probability. Third, the relapse cost. Fourth, which is likely to be typographical, inputs repository cells E14 and F14, the column headings upper 95% CI and Lower 95% CI. No change made.

Page 28 of the ERG Report states: *"The CS later describes three DMTs which are licensed for RRMS (ocrelizumab, cladribine and interferon β-1a)"* This statement is incorrect. The three DMTs ocrelizumab, cladribine and interferon β-1a are licensed for relapsing MS (RMS), rather than solely relapsing-remitting MS (RRMS).	The statement on page 28 should be corrected to: *"The CS later describes three DMTs which are licensed for RMS (ocrelizumab, cladribine and interferon β-1a)"*	The current statement is currently incorrect based on the EMA licences of the three DMTs.	The ERG agree with this factual error. We will amend to state the following: *"RMS"*
Page 57 of the ERG Report states: *"Additional subgroups not specific to the primary endpoint were:* • *Time to 3-month confirmed worsening in T25FW of at least 20%* • *Change from baseline in T2 lesion volume* • *Time to 6-month CDP* • *ARR"* This wording is currently unclear.	To clarify the subgroup analyses performed, the wording should be replaced with the following: *"Additional subgroup analyses were conducted for the following endpoints:* • *Time to 3-month confirmed worsening in T25FW of at least 20%* • *Change from baseline in T2 lesion volume* • *Time to 6-month CDP* • *ARR"*	The current statement is unclear.	The ERG agree that the following sentence can be amended for clarity: *"Additional subgroup analyses were conducted for the following endpoints"*

Page 72 and 74 of the ERG Report states: *"…there is considerable overlap in hazard ratios across levels of the stratification variables, which suggests that important effect modification is not occurring."* and *"the overlap between groups for each EM suggests that the variables the company present as EM could be contested."* This is incorrect. Non-significance should not be interpreted as lack of treatment effect modification given the loss of power associated with estimating treatment effects between sub-populations from clinical trials. If there were no treatment effect modifiers present, there would not have been profound swings in the effect estimates among the various scenarios in MAIC. The largest swings arise in the matching step that was based on differences in the eligibility of trials. For example, prior history of treatment with IFNβ (usually a disqualifying criterion in comparator trials) has been shown to be an unequivocal treatment effect modifier.	Both statements should be removed.	The current statements are incorrect.	The ERG note the comment but do not consider it to be a factual error. The ERG further note that non-significance is based on all of the data the company have for the EXPAND trial, not just for a subset of the total sample. In the ESS tables of Scenarios A-F in CS Appendix D, (where the adjustments for EMs were performed), there were not any 'profound' swings in estimates except for IMPACT. However, for clarity we have made the following amendments: "*…there is considerable overlap in hazard ratios across levels of the stratification variables. Given the wide CIs the interpretation is limited regarding the presence of any effect modification"* and *"The overlap between groups and wide CIs for each EM limits the interpretation of the variables the company present as EM"*

Page 77 of the ERG Report states: *"In the adjustment step, patients in the EXPAND trial IPD were re-weighted to make the distribution of important EM (baseline patient characteristics) in the sample source similar to those in the competitor trials' treatment arms (e.g., natalizumab arm in ASCEND study). The weights (i.e., propensity scores) were estimated as the odds of being in the siponimod arm (in EXPAND study) versus the treatment arm (e.g., natalizumab) of the competitor trial (e.g., ASCEND study) in a regression model adjusted for all EM using the generalised method of moments based on IPD and aggregate data."* These statements on the CS MAIC are incorrect. The re-weighting aligns the characteristic to that of the comparator study's entire population, not specifically to the active treatment arm. The propensity scores were the estimated odds of being in EXPAND vs. the comparator trial, not specifically the treatment arms.	This statement on Page 77 should be amended as follows to accurately reflect the CS MAIC: *"In the adjustment step, patients in the EXPAND trial IPD were re-weighted to make the distribution of important EM (baseline patient characteristics) in the sample source similar to those in the competitor trials (e.g., ASCEND). The weights (i.e., propensity scores) were estimated as the odds of being in the EXPAND study versus the competitor trial (e.g., ASCEND)."*	The current statement is incorrect.	The ERG agree with this factual error and have amended the following sentence: *"in the competitor trials (e.g., ASCEND). The weights (i.e., propensity scores) were estimated as the odds of being in the EXPAND study versus the competitor trial"*

Page 93 of the ERG report states: *"The company used 10% limit and SMD=0.1 threshold to operationalise their decisions when comparing baseline characteristics across the studies. The impact of the decisions based on these arbitrary rather than empirically-based thresholds is difficult to determine"* This is incorrect. As reported in CS Document B, page 67: *"For quantitative values, a threshold of +/-10% was chosen to determine whether a characteristic was similar (<10% difference in either direction) or dissimilar (>10% difference in either direction) to EXPAND. This was a subjective judgement and a difference of greater than 10% does not necessarily indicate that the characteristic in question is a driver for bias. A characteristic greater than the 10% threshold was flagged as dissimilar and considered as a potential source of heterogeneity and/or bias, which could present a weakness of indirect comparisons. For quantitative analyses, characteristics were adjusted for irrespective of whether a 10% threshold was observed."* The 10% threshold was not used to decide on the approach in analyses. It was used only to qualitatively assist in examining and communicating whether the trials were different. Without using the 10% threshold, it is still clear and apparent the trials differ substantially in some key eligibility criteria and baseline patient characteristics. For example, for prior history of IFNβ treatment, this was permitted in the ASCEND trial (but not within the prior 4 weeks) and EXPAND trial (approximately [redacted] of patients were IFN-experienced), whereas prior history was not permitted in the North American Study, European Study, IMPACT, and SPECTRIMS (i.e. 0% of patients in these trials were IFN-experienced). As reported in CS Document B, page 70: *"SMD were also used to quantify the degree of heterogeneity between the trials for each baseline characteristic when compared to EXPAND."* The SMD approach was used in addition to the 10% threshold as there are literature-reported, recognised thresholds identified in contrast to the arbitrariness of the 10% threshold. However, again, this was not used to determine the analytical approach and operationalise decisions, but as an assist for displaying and communicating the differences between trials.	The statement on Page 93 should be removed.	The current statement is incorrect.	The ERG appreciates the comment but we do not consider it to be a factual error, rather a misplacement of text. The thresholds described were not used in decision making while performing the MAIC. They were used in the assessment of NMA feasibility. Therefore, we have moved the sentence out of summary section 4.4.2 and into the previous section 4.4.1.1 which described the feasibility assessment for NMA. The sentence already states that the company used both the 10% and SMD threshold (based on point 2 in B.2.9 "*Heterogeneity between EXPAND and comparator trials was identified by pairwise comparisons and standardised mean difference (SMD) test of trial characteristics.")*

Page 95 of the ERG Report states: *"The target population for siponimod was defined as patients diagnosed with relapsing forms of MS, including RRMS and active SPMS in whom siponimod and DMTs are likely to be indicated or recommended."* This statement is incorrect. The target population for siponimod was defined as per the decision problem (CS Document B, Table 1, Page 12) which states: *"Adults with SPMS."*	This consideration from the ERG should be amended in light of the target population stated in the CS decision problem.	The target population currently stated is incorrect.	The ERG agree that this is an error and could be changed to align to the decision problem. We will amend the following: *"Adults with SPMS."*
Page 95 of the ERG Report states: *"However, the ERG note that the interferon-β 1b trial (EU study) contains a historic population sample (published in 1998 and 2001), which is considerably older than the more recent EXPAND study (2018)."* The use of "older" terminology could cause confusion between the publication year of the trial or age of patients.	The statement on Page 95 should be reworded as follows, to clarify that this is referring to the publication year of the trial, rather than age of patients: *"However, the ERG note that the interferon-β 1b trial (EU study) contains an historic population sample (published in 1998 and 2001). This represents a considerably older study compared to the more recent EXPAND study (published in 2018)."*	The wording in the current statement is unclear.	The ERG agree that the following sentence should be amended for clarity: *"However, the ERG note that the interferon-β 1b trial (EU study) contains a historic population sample as the studies were published in 1998 and 2001, therefore considerably older than the more recent EXPAND study which was published in 2018."*

Page 101 of the ERG Report state: *"The ERG note that the two interventions in the NA study (interferon β-1b) and EXPAND (siponimod) are owned by the company. Therefore, we consider it possible to conduct a valid IPD meta-analysis of the data with appropriate adjustments to account for imbalances across arms. However, the company chose not to do this and instead carried out a MAIC analysis despite the considerable uncertainties and stronger assumptions around such analysis."* These statements are incorrect. As detailed in Novartis' response to ERG clarification question A16, Novartis has a commercial arrangement with Bayer Pharma to market a version of interferon β-1b. However, Novartis did not originally develop interferon β-1b and do not own the NA study data, and therefore does not have access to IPD to perform a meta-analysis.	The following paragraph on Page 101 should be removed: *"The ERG note that the two interventions in the NA study (interferon β-1b) and EXPAND (siponimod) are owned by the company. Therefore, we consider it possible to conduct a valid IPD meta-analysis of the data with appropriate adjustments to account for imbalances across arms. However, the company chose not to do this and instead carried out a MAIC analysis despite the considerable uncertainties and stronger assumptions around such analysis."*	The current statement on Page 101 is incorrect and conflicts with Novartis' response to ERG clarification question A16.	The ERG appreciate this comment. However, this is not a factual inaccuracy. We note that we have already made reference to the company response to A16 in the ERG report. No change made.
Page 126 of the ERG Report presents the NICE reference case checklist for the economic evaluation. The Comparators row states: *"Comparator included in the base-case was interferon β-1b. Scenario analyses included other DMTs used outside of their marketing authorisations."* This statement is incorrect. The RRMS DMTs in the scenario analyses were not considered outside of their marketing authorisation, but instead were considered as clinicians tend to continue the use of DMTs in light of suspected SPMS (prior to confirming a formal diagnosis of SPMS) because of the uncertainty in identifying the transition from RRMS to SPMS (CS Document B.1.3.1).	The following should be removed from the statement on Pages 126, 181 and two statements on Page 129: *"used outside of their marketing authorisations."*	The current statements are not reflective of the CS or of UK clinical practice.	The ERG do not consider this to be a factual error and note that this is the terminology used by NICE in the final scope No change made.

Page 127 of the ERG Report states: *"Though not explicitly stated in the CS, it was assumed that the cohort all had either the CYP2C9*1*3 or *1*3 genotype"* This statement includes the same CYP2C9 genotype twice.	Please could the ERG clarify their assumption regarding the CYP2C9 genotype of the cohort of people in the model with SPMS.	The current statement includes an error.	The ERG agree that this is a factual error. We will amend the following: *"CYP2C9*2*3 or *1*3"*
Page 130 of the ERG Report states: *"The ERG noted that there were some differences between the starting populations/distributions in the CS document compared to the ICER 2019 report, even though there were derived from the EXPAND trial. The ERG were unable to understand or explain why these differences exist."* Please note, the only differences in the starting populations/distributions between the CS and ICER 2019 report are for EDSS 3/4: • In the Kappos et al. 2018 publication for EXPAND, EDSS 3/4 are reported as one group (28% of patients). To report this as two groups, ICER simply provided a 50:50 split (i.e. 14% for both EDSS 3 and 4). • Novartis had more granular EXPAND data available, and was therefore able to provide the accurate split between EDSS 3/4 ([redacted] %, [redacted] %, respectively).	The following statement should be removed: *"The ERG noted that there were some differences between the starting populations/distributions in the CS document compared to the ICER 2019 report, even though there were derived from the EXPAND trial. The ERG were unable to understand or explain why these differences exist."*	The differences in the starting populations distributions between the CS and ICER 2019 are easily explained upon review of the data, and therefore do not represent a concern.	The ERG would like to thank the company for providing an explanation as to why there appear to be differences between the starting populations. However, we do not consider this a factual error. No change made.

Page 131 of the ERG Report states: *"In discussion with the ERG clinical advisor, we understand that over the long-term, people with SPMS will progress (or rarely plateau); but in the short-term, if people have a relapse from which they recover they could improve before they worsen again. The ERG have made the assumption that the short timeframe is approximatley 2-3 months. However, the transitions in the model are yearly, thus making regressions very rare or impossible."* The last statement is factually inaccurate. Data from the EXPAND placebo arm demonstrate evidence for the possibility of regression, as discussed on Page 117 of the CS. This evidence of regression from EXPAND data led to Novartis' decision to use transition probabilities from EXPAND, supplemented with London Ontario.	The following statement should be removed: *"However, the transitions in the model are yearly, thus making regressions very rare or impossible."*	The current statement is factually inaccurate.	The ERG appreciate this comment, we will amend the sentence to state the following: "*However, the transitions in the model are yearly, thus making regressions very rare."*

Page 132 of the ERG Report states: *"First, the transition matrix derived from the London Ontario dataset alone shows that there are no regressions (or reductions in disability) and disability scores for people can only worsen over time."* This is incorrect. The London Ontario dataset enforced an analytic rule that there could be no regression. As stated in Palace et al. (2014):[1] "*The natural history cohort (from London, Ontario, Canada) was unexpectedly found to contain retrospectively smoothed disability data (rather than actual, real-time collected disability scores), censoring any improvement in EDSS. Comparing our uncensored treated cohort to data retrospectively smoothed in this way would have the effect of unpredictably underestimating any treatment effect.*"	This statement should be corrected to the following: *"The London Ontario dataset enforced an analytic rule that there could be no regression (or reductions in disability), so disability scores for people can only worsen over time."* Please could the ERG also remove or reconsider the following statement in light of the above: *"The ERG considers the London Ontario database to be more appropriate."*	The current statement is incorrect.	The ERG appreciate this comment, we will amend the first sentence to state the following: "*The London Ontario dataset enforced an analytic rule that there could be no regression (or reductions in disability), so disability scores for people can only worsen over time*." The other statement remains.

[1] Palace J, Bregenzer T, Tremlett H, et al. UK multiple sclerosis risk-sharing scheme: a new natural history dataset and an improved Markov model. BMJ Open 2014;4:e004073. doi: 10.1136/bmjopen-2013-004073

Page 140 of the ERG Report states: *"These results suggest that treatment with siponimod is expected to yield 3.17 relapses (not requiring hospitalisation) per annum per person compared to 3.30 for people undergoing treatment with interferon β-1b. Treatment with siponimod is expected to yield 0.07 fewer relapses requiring hospitalisation compared to interferon β-1b."* This statement is incorrect – the figures for relapses per person are not per annum, but are instead over the model time horizon (i.e. lifetime).	This statement on Page 140 should be amended as follows: *"These results suggest that, **over the model time horizon**, treatment with siponimod is expected to yield 3.17 relapses (not requiring hospitalisation) per person compared to 3.30 for people undergoing treatment with interferon β-1b. Treatment with siponimod is expected to yield 0.07 fewer relapses requiring hospitalisation compared to interferon β-1b."* Similarly, the caption for Table 52 should be amended as follows: *"Model output for the expected yield of relapses per person **over the model time horizon**"*	The current references to relapses per annum are incorrect.	The ERG consider this to be a factual error and have amended the text suggested by the company. *"These results suggest that, **over the model time horizon**"* The caption for Table 52 has been amended as follows: *"Model output for the expected yield of relapses per person **over the model time horizon**"*
Page 142 of the ERG Report states: *"Caregiver's disutilities used in the base-case were obtained from Gani et al.,(2008)…The ERG consider it more appropriate to use the disutilities obtained from TA127 as these are more in line with our expectation that disutilities increase as the EDSS severity increases."*	Please note, the disutilities from Gani et al. (2008) and TA127 are the same. For clarity, the statement should therefore be amended to: *"Caregiver's disutilities used in the base-case were obtained from Gani et al.,(2008), which were also used in TA127…The ERG consider it more appropriate to use the disutilities obtained from TA127 as these are more in line with our expectation that disutilities increase as the EDSS severity increases."*	The current statement does not specify that disutilities from Gani et al. (2008) and TA127 are the same.	The ERG do not consider this a factual error, but will amend for clarity. *"Caregiver's disutilities used in the base-case were obtained from Gani et al.,(2008), **which were also used in TA127**…"*

Page 152−153 of the ERG Report state: *"…using the lower estimate (making siponimod less effective) resulted in an ICER of approximately [redacted] per QALY."* This is incorrect. Using the lower estimate of the HR for 6-month CDP would make siponimod *more* effective.	This statement should be corrected to: *"…using the lower estimate (making siponimod more effective) resulted in an ICER of approximately [redacted] per QALY."*	The current statement is factually incorrect.	The ERG consider this to be a factual error and have amended the following text: *"…using the lower estimate (making siponimod more effective) resulted in an ICER of approximately [redacted] per QALY."*
Row 2 of Table 65, Page 157 of the ERG Report states: *"It should be noted that these results reported by the company are for people with RRMS."* This is incorrect. The North American Study was used for treatment efficacy of interferon β-1b, which included subjects with SPMS only.	This statement should be removed.	The current statement is incorrect.	The ERG consider this to be a factual error and have removed this statement.

Issue 2 General Errors

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 15 of the ERG Report lists the outcomes in which siponimod displayed a significant improvement compared with placebo. The following bullet point requires a timepoint: *"Between-group difference in the mean Multiple Sclerosis Walking Test (MSWS-12) score change from baseline at 12 (-1.83; 95% CI: -3.85, 0.19)"*	The bullet point should be amended to specify the change from baseline at 12 *months:* *"Between-group difference in the mean Multiple Sclerosis Walking Test (MSWS-12) score change from baseline at 12* ***months*** *(-1.83; 95% CI: -3.85, 0.19)"*	The MSWS-12 endpoint is currently not correctly and fully explained.	The ERG agree that the following sentence should be amended for clarity: *"Between-group difference in the mean Multiple Sclerosis Walking Test (MSWS-12) score change from baseline at 12* ***months*** *(-1.83; 95% CI: -3.85, 0.19)"*
Page 18 of the ERG Report states: *"The ERG are concerned that the ESS represents a substantial drop from the randomised sample size of EXPAND (1651), and the sample included in the statistical analysis (1646)."* The sample size included in the statistical analysis is incorrect, this value should be 1,645 (1,099 in the siponimod group; 546 in the placebo group) as per the CS and Kappos et al. EXPAND publication.	The sample size for the statistical analysis should be amended to 1,645, on both Page 18 and Page 81.	The current data value is incorrect.	The ERG agree that this is a factual error. We will amend the following on pages 18 and 81: *"1,645"*

Page 55 of the ERG Report presents data for the change from baseline of the MSIS-29 psychological impact scores: *"The overall change from baseline of the MSIS-29 psychological impact scores was significantly [redacted] in the siponimod group compared to the placebo group (mean difference: [redacted]; 95% CI: [redacted] to [redacted] p = [redacted])."* The p value given is incorrect. The value for the MSIS-29 physical impact scores has incorrectly been provided, and should instead be [redacted], as per Table 112, Page 599 in CS Appendices.	The results should be corrected to: *"The overall change from baseline of the MSIS-29 psychological impact scores was significantly [redacted] in the siponimod group compared to the placebo group (mean difference: [redacted]; 95% CI: [redacted] to [redacted]; p = [redacted])."*	The current data value provided is incorrect.	The ERG agree that this is a factual error. We will amend the following p value on page 55: "*p = [redacted])."*
Table 12, Page 61 of the ERG Report presents the numbers of patients discontinuing treatment after reaching 6-month CDP. The column for placebo is labelled as: "*Placebo N=649 n (%)"* This is incorrect. The value for N should be 546, as per Table 10-2, Page 88 of the CSR.	The columns header should be corrected to: *"Placebo N=546 n (%)"*	The current data value provided is incorrect.	The ERG agree that this is a factual error. We will amend the following: *"N=546"*

Table 13, Page 62 of the ERG Report presents the adverse event safety outcomes from the EXPAND trial publication. The numbers of patients discontinued because of an adverse event are reported as: "*84 (8%), of which 48 were serious and 36 non-serious*" for siponimod "*28 (5%), of which 15 were serious and 13 non-serious*" for placebo. These are incorrect. The values for serious and non-serious have been reported the wrong way around.	The results should be corrected to: *"84 (8%), of which 36 were serious and 48 non-serious*" for siponimod "*28 (5%), of which 13 were serious and 15 non-serious*" for placebo.	The current data provided are incorrect.	The ERG agree that this is a factual error. We will amend the following sentences: *"84 (8%), of which 36 were serious and 48 non-serious*" for siponimod "*28 (5%), of which 13 were serious and 15 non-serious*" for placebo.
Table 17, Page 71 of the ERG Report presents the baseline characteristics of the trials included in the MAIC analyses. There is no reported value for "*proportion of patients with Gd+ lesions of T1-weighted images (%)"* for the column "*IMPACT"* This is incorrect. There should be a value of 36 for this cell, as per Table 37 of the CS Document B.	The value for "*proportion of patients with Gd+ lesions of T1-weighted images (%)"* for the column "*IMPACT"* should be updated from "*NA"* to "*36".*	The current data value provided is incorrect.	The ERG agree that this is a factual error. We will amend the following: "*36".*
Page 105 of the ERG Report discusses the results of the MAIC for siponimod versus interferon β-1a, reporting the following values: *"([redacted] vs. HR 0.81 95% CI: 0.54, 1.22)"* The value for the first confidence interval is incorrect, and should instead be [redacted], as per Table 41, Page 76 of the CS Document B.	The value for the confidence interval should be corrected to: *"([redacted] vs. HR 0.81 95% CI: 0.54, 1.22)"*	The current data value provided is incorrect.	The ERG agree that this is a factual error. We will amend the following: *"([redacted] vs. HR 0.81 95% CI: 0.54, 1.22)"*

Table 42, Page 126 of the ERG Report presents the NICE reference case checklist for the economic evaluation. The Time horizon row states: *"50-year time horizon"* This is incorrect. The company model used a lifetime time horizon. This equated to 53 model cycles in the base case analysis, which is dependent on the cohort starting age and a maximum lifespan of 100 years (dictated by availability of ONS mortality data).	This should be corrected in Table 42, Page 126 and on Page 135 to state: *"Lifetime time horizon"*	The time horizon currently stated is incorrect.	The ERG agree that this is a factual error. We will amend the following: *"Lifetime time horizon"*
Page 137 of the ERG Report states: *"These relative risks for 6-month CDP were based on the results from the North American study, which compared siponimod versus placebo (HR= 0.92, 95% CI: 0.71, 1.20), and the MAIC analysis for siponimod versus placebo (HR=0.50, 95% CI: 0.32, 0.78). To our knowledge the model does not directly use the 6-month CDP HR derived from the MAIC (HR= 0.55, 95% CI: 0.33, 0.91) for the comparison between siponimod and interferon β-1b (Extavia®). This relative risk was applied as a probability to forward transitions, and it was assumed that the relative risk remain constant for the duration of the model, once on treatment."* The reference to relative risks is incorrect. The hazard ratio (HR) was used as the effect estimate for time to 6-month CDP from the MAIC analysis.	Reference to *"relative risk"* should be replaced with *"hazard ratio*" when discussing the effect estimates for time to 6-month CDP.	The reference to relative risks is incorrect.	The ERG agree that this is a factual error. We will amend the following: *"hazard ratio*"

The Treatment discontinuation row of Table 62, Page 153 of the ERG currently states *"Time-dependent"* for both the base-case analysis and scenario analysis. This is incorrect: the base-case used time-dependent discontinuation, however the scenario analysis used time-*independent*.	*"Time-dependent"* should be corrected to *"time-independent"* in the Scenario analysis column.	The Treatment discontinuation is currently incorrect for the scenario analysis.	The ERG agree that this is a factual error. We will amend the following: *"time-independent"*
Table 64, Page 156 of the ERG Report present the company's scenario analyses results. The total QALYs for teriflunomide is incorrectly reported as 3.71. This value is 3.01 in CS Document B Table 77.	The 3.71 total QALYs value for teriflunomide should be corrected to 3.01 in Table 64.	This data value has been copied incorrectly from CS Document B and the cost-effectiveness model.	The ERG agree that this is a factual error. We will amend the following: *" 3.01 "*
Page 163 of the ERG Report states: *"Using the cost of £4,357 for treating adverse events obtained from TA527 – RSS model and ScHARR analysis."* This is incorrect. The cost of £4,357 is for treating *relapses*, not adverse events.	The statement should be reworded to: *"Using the cost of £4,357 for treating **relapses** obtained from TA52778 – RSS model and ScHARR analysis."*	The current statement is incorrect.	The ERG agree that this is a factual error. We will amend the following: *"Using the cost of £4,357 for treating **relapses** obtained from TA52778 – RSS model and ScHARR analysis."*

Issue 3 Confidentiality Marking

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 41 of the ERG Report presents data from the CSR around patients excluded from the trial at screening. The value for the number of patients screened is missing AIC highlighting.	Add yellow AIC highlighting to the value [redacted] on Page 41.	These are unpublished data from the EXPAND clinical trial. Publication date is not yet determined, but it is anticipated that the information will be in public domain by end of 2021.	The ERG will amend this error.
Page 44 of the ERG Report discusses the generalisability of the EXPAND trial to the UK population. The proportion of patients in the UK who identify as White is incorrectly marked as AIC.	Remove the yellow AIC highlighting for the value "*UK (86.0%)"* on Page 44.	NICE guidelines state that ACIC marking should be kept to a minimum. This value is not confidential as it is sourced from published material.	The ERG will amend this error. We have also removed the underline.
Page 52 of the ERG Report presents data for the change from baseline of percentage brain volume. The rate reductions at 12 months post-baseline (0.175) and 24 months post-baseline (0.128) are incorrectly marked as AIC.	Remove the yellow AIC highlighting for the following value on Page 52: *"at 12 months post-baseline (rate reduction 0.175; 95% CI: 0.103 to 0.247; p < 0.0001); at 24 months (rate reduction 0.128; 95% CI: 0.021 to 0.236; p < 0.0001)"*	NICE guidelines state that ACIC marking should be kept to a minimum. These values are not confidential.	The ERG will amend this error. We have also removed the underline.
Page 59 of the ERG Report presents the results for adjusted ARR for confirmed relapses. The 95% confidence interval and p value for the ARR ratio are missing AIC highlighting.	Add yellow AIC highlighting to the 95% CI and p value given for ARR on Page 59: *"(ARR ratio: [redacted]; 95% CI: [redacted] to [redacted]; p = [redacted])"*	These are unpublished data from the EXPAND clinical trial. Publication date is not yet determined, but it is anticipated that the information will be in public domain by end of 2021.	The ERG will amend this error.

Table 11, Page 60 of the ERG Report presents the results for the primary and secondary endpoints for the active SPMS subgroup. The value for the number of patients with relapse events for the placebo arm is missing AIC highlighting.	Add yellow AIC highlighting to the [redacted] value for "*Number with events (%)*" for the placebo arm in Table 11.	These are unpublished data from the EXPAND clinical trial. Publication date is not yet determined, but it is anticipated that the information will be in public domain by end of 2021.	The ERG will amend this error.
Table 17, Page 71 of the ERG Report presents the baseline characteristics of the trials included in the MAIC analyses. A number of data values for the EXPAND trial have been underlined but are missing AIC highlighting: • "*Proportion of patients without previous use of a DMT (%)"* • *"Time since most recent relapse (months)"* • *"Proportion of patients relapse-free in prior year (%)"* • *"Proportion of patients relapse-free in prior 2 years (%)"*	Add yellow AIC highlighting to the values under the column EXPAND in Table 17 for the following rows: • "*Proportion of patients without previous use of a DMT (%)"* – [redacted] • *"Time since most recent relapse (months)"* – [redacted] • *"Proportion of patients relapse-free in prior year (%)"* – [redacted] • *"Proportion of patients relapse-free in prior 2 years (%)"* – [redacted]	These are unpublished data from the EXPAND clinical trial. Publication date is not yet determined, but it is anticipated that the information will be in public domain by end of 2021.	The ERG will amend this error.
Page 81 of the ERG Report discusses the sample sizes of the unmatched and unadjusted, and matched (but unadjusted) populations from the MAIC analyses. These sample size numbers throughout the final paragraph of Page 81 are missing AIC highlighting. As noted above, the 1,646 figure should be corrected to 1,645.	Add yellow AIC highlighting to the following sample size values on Page 81: *"from 1645 patients included in the analysis to [redacted] in scenario A"* *"from [redacted] to the ESS [redacted] patients"*	These are unpublished data from the MAIC analyses. Publication date is not yet determined, but it is anticipated that the information will be in public domain by end of 2021.	The ERG will amend this error.

Table 28, Page 90 of the ERG Report presents a summary of the MAIC results for 3- and 6-month CDP. The data in the column for the EXPAND study sample size are missing AIC highlighting.	Add yellow AIC highlighting to all values under the heading *"Sample Size, EXPAND study"* in Table 28.	These are unpublished data from the MAIC analyses. Publication date is not yet determined, but it is anticipated that the information will be in public domain by end of 2021.	The ERG will amend this error.
Table 29, Page 91 of the ERG Report presents a summary of the MAIC results for ARR. The data in the column for the EXPAND study sample size are missing AIC highlighting.	Add yellow AIC highlighting to all values under the heading *"Sample Size, EXPAND study"* in Table 29.	These are unpublished data from the MAIC analyses. Publication date is not yet determined, but it is anticipated that the information will be in public domain by end of 2021.	The ERG will amend this error.
Table 30, Page 97 of the ERG Report presents a summary of the published effectiveness estimates for all trials included in the MAIC analyses. The 95% confidence intervals for the hazard ratio of the proportion of patients with 6-month CDP for the EXPAND trial are missing AIC highlighting.	Add yellow highlighting to the 95% CI values for the row for EXPAND under the heading "*Proportion with 6-month CDP (96w)"* in Table 97.	These are unpublished data from the EXPAND clinical trial. Publication date is not yet determined, but it is anticipated that the information will be in public domain by end of 2021.	The ERG will amend this error.
Table 48, Page 134 of the ERG Report presents the natural history ARR data used in the economic model. All data values are correct, however the Patzold and Pocklington (1982) and UK MS Survey values in the third column have incorrectly been marked as AIC.	Remove the yellow AIC highlighting in the third column for Patzold and Pocklington (1982) and UK MS Survey.	NICE guidelines state that ACIC marking should be kept to a minimum. These values are not confidential.	The ERG will amend this error. We have also removed the underline.
Table 60, Page 149 of the ERG Report presents the company's base-case deterministic results. The value for incremental LYG for siponimod vs Interferon β-1b (0.30) has incorrectly been marked as CIC.	Remove the blue CIC highlighting for the 0.30 figure in Table 60.	NICE guidelines state that ACIC marking should be kept to a minimum. This value is not confidential.	The ERG will amend this error. We have also removed the underline.

Table 64, Page 156 of the ERG Report present the company's scenario analyses results. The total cost for natalizumab (£347,414) is incorrectly marked as CIC.	Remove the blue CIC highlighting for the £347,414 for natalizumab in Table 64.	NICE guidelines state that ACIC marking should be kept to a minimum. This value is not confidential.	The ERG will amend this error. We have also removed the underline.

Issue 4 Typographical Errors

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG Report misspells *"trial"* as *"trail"* on the following pages: Pages 39, 59, 96	*"Trail"* should be corrected to *"trial"*.	This is a typographical error.	Agree. The ERG will amend this error.
The ERG Report misspells *"starting"* as *"staring"* on Page 60.	*"Staring"* should be corrected to *"starting"*.	This is a typographical error.	Agree. The ERG will amend this error.
The ERG Report misspells *"6-month"* as *"6-monthh"* on Page 98 and Page 176.	*"6-monthh"* should be corrected to *"6-month"*.	This is a typographical error.	Agree. The ERG will amend this error.
The ERG Report misspells *"approximately"* as "*approximatley"* on Page 130.	*"Approximatley"* should be corrected to *"approximately"*.	This is a typographical error.	Agree. The ERG will amend this error.
The Transition probabilities row of Table 59, Page 147 of the ERG Report contains a typographic error: *"Recent technology appraisals have included a natural history transition matrix, which does not allow for a re disability."*	This sentence should be corrected to: *"Recent technology appraisals have included a natural history transition matrix, which does not allow for a* ***regression*** *in disability."*	This is a typographical error.	Agree. The ERG will amend this error.

The ERG Report misspells *"siponimod"* as *"sipnoimod"* on Page 151 and as *"siponoimod"* on Page 153.	These two instances of the incorrect spelling of siponimod should be corrected.	This is a typographical error.	Agree. The ERG will amend this error.
The ERG Report misspells *"natalizumab"* as *"natlizumab"* on Page 156.	*"Natlizumab"* should be corrected to *"natalizumab"*.	This is a typographical error.	Agree. The ERG will amend this error.
The ERG Report does not capitalise *"Extavia®"* on Page 162 and 166.	*"Extavia®"* is a brand name and should be capitalised on Page 162 and 166.	This is a typographical error.	Agree. The ERG will amend this error.
The ERG Report misspells *"demonstrated"* as *"desmonstrated"* on Page 178.	*"Desmonstrated"* should be corrected to *"demonstrated"*.	This is a typographical error.	Agree. The ERG will amend this error.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Technical report

Siponimod for treating secondary progressive multiple sclerosis

Summary of the technical report

This document is the technical report for this appraisal. It has been prepared by the technical team with input from the lead team and chair of the appraisal committee.

The technical report and stakeholder's responses to it are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the appraisal committee meeting.

The technical report includes:

- a commentary on the evidence received and written statements
- technical judgements on the evidence by the technical team
- reflections on NICE's structured decision-making framework.

This report is based on:

- the evidence and views submitted by the company, consultees and their nominated clinical experts and patient experts and
- the evidence review group (ERG) report.

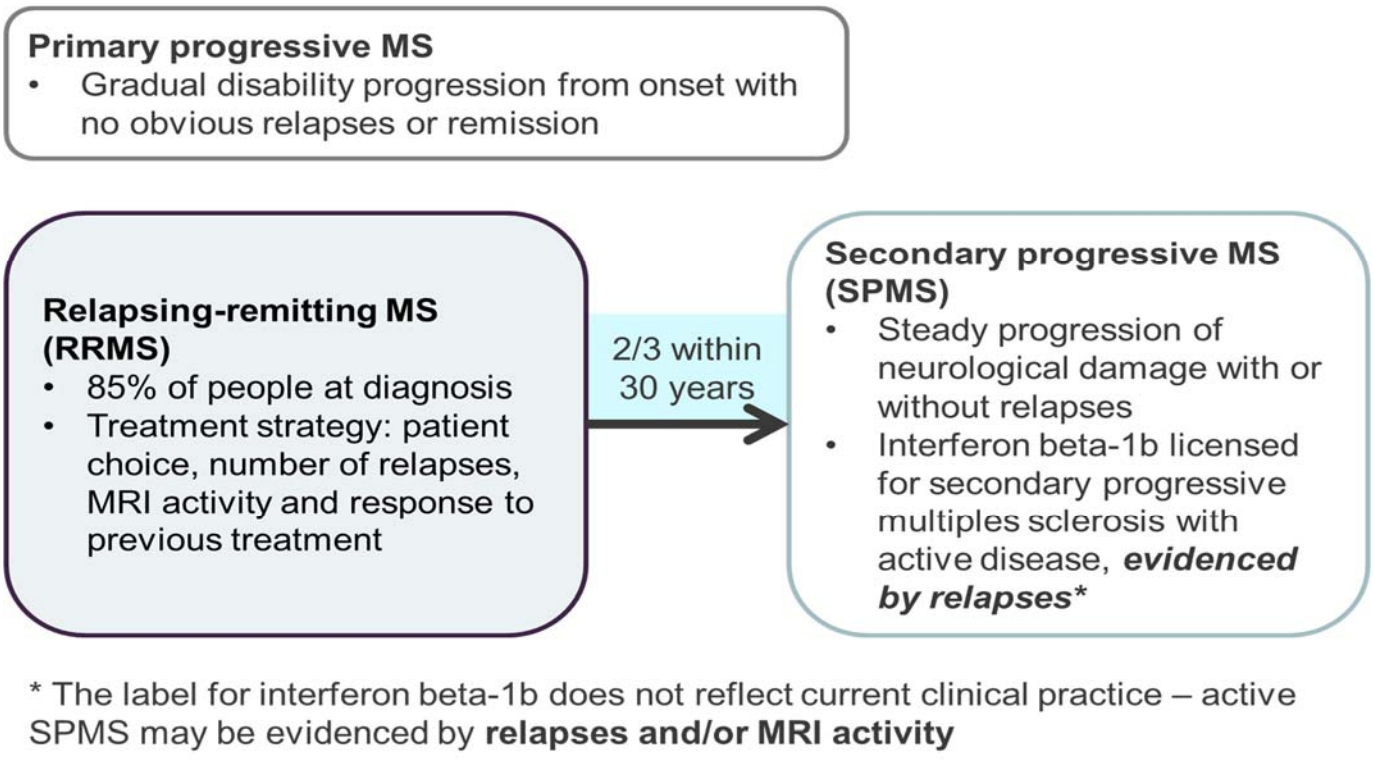
The technical report should be read with the full supporting documents for this appraisal.

1. Topic background

1.1 Disease background: multiple sclerosis (MS)

- Chronic, lifelong, neurological disease with no cure, resulting in progressive, irreversible disability
- Affects central nervous system:
    - immune system mistakenly attacks myelin sheath (layer that surrounds and protects nerves), disrupting signals travelling along the nerves
- Associated with pain, chronic fatigue, unsteady gait, speech problems, incontinence, visual disturbance and cognitive impairment
- Onset typically between 25 and 35 years of age
- Secondary progressive MS characterised by more persistent or gradually increasing disability
    - associated with lower mobility, higher levels of depression/anxiety and greater dependence on caregivers than relapsing-remitting MS
- Approximately 110,000 people in UK have MS, 43,000 secondary progressive
    - 2/3 with relapsing-remitting transition to secondary progressive over 30yrs

1.2 Types of multiple sclerosis



* The label for interferon beta-1b does not reflect current clinical practice – active SPMS may be evidenced by **relapses and/or MRI activity**

1.3 Information about siponimod

- **Committee for Medicinal Products for Human Use positive opinion:** "treatment of adult patients with secondary progressive MS with active disease evidenced by relapses or imaging features of inflammatory activity"
  - trial: relapses in 2 years prior to study or gadolinium-enhanced T1 lesions at baseline

  Original submission and key trial include broader population "secondary progressive MS" i.e. some did not have active disease
- **Administration and dose:** 6-day titration period then maintenance treatment with 1x2 mg tablet taken once daily
- **Additional tests:** genotype test to determine CYP2C9 metaboliser status
  - small number with certain genotypes may require a lower maintenance dose or siponimod may not be suitable
  - company to fund genotyping service
- **Cost:** patient access scheme discount agreed; annual cost: [redacted]

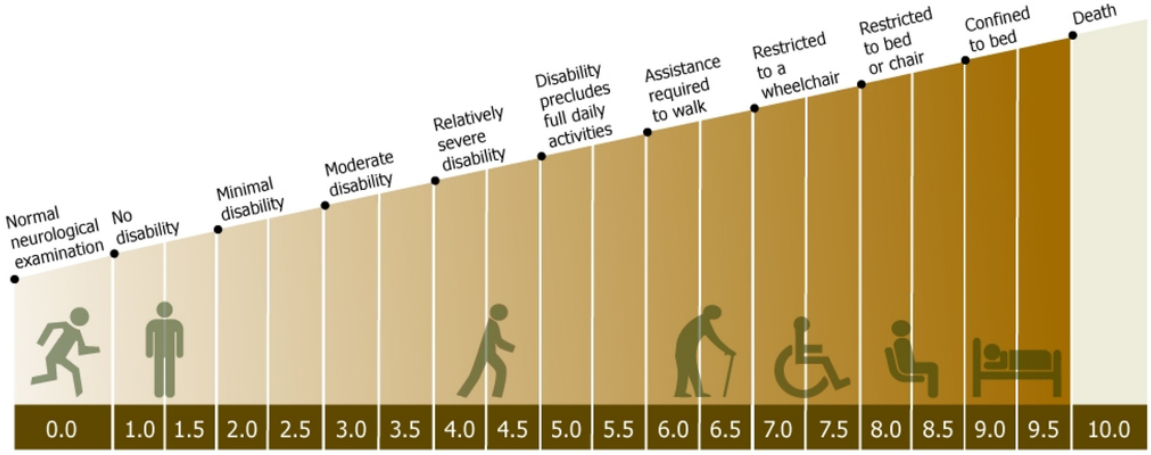
1.4 Decision problem

	Final scope	Company submission	Notes
Population	People with secondary progressive MS		Anticipated marketing authorisation is for "**active disease**"
Subgroups	Active secondary progressive MS, evidenced by relapses		**Subgroup analysis aligned with anticipated marketing authorisation**
Comparators	• Established clinical management, including treatments licensed for relapsing-remitting MS used outside their marketing authorisations • Interferon β-1b (Extavia) for patients with active disease	• Established clinical management, including treatments licensed for relapsing-remitting MS used outside their marketing authorisations • Interferon β-1b for patients with active disease, evidenced by relapses **and/or MRI activity**	• Company analysis for **subgroup with active disease** compares with interferon β-1b • Company did not compare with other treatments licensed for relapsing-remitting MS used outside their marketing authorisations for this population: stated that results compared with interferon β-1b could be considered a conservative estimate for other interferons. This is because *"TA527 indicates that Extavia is the lowest-cost interferon (based on equal efficacy of interferons and also glatiramer acetate)"*

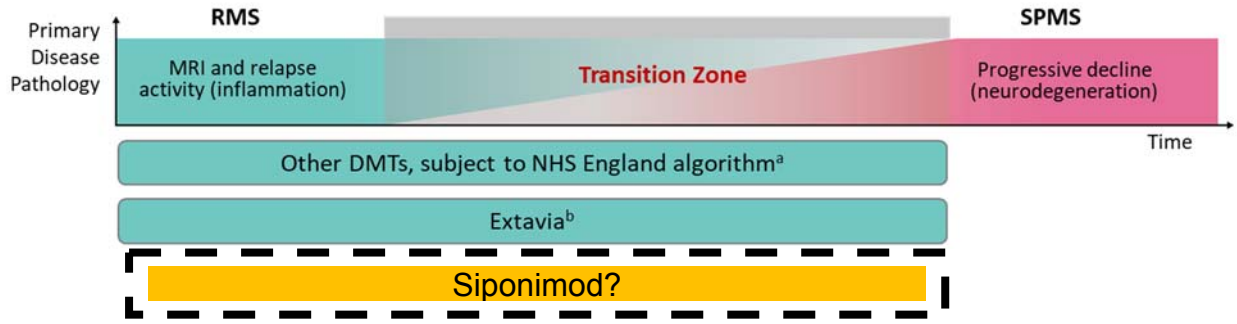
1.5 Outcome definitions

- Relapse: new or recurrent neurological symptoms lasting ≥24 hours without fever or infection; separate events are at least 30 days apart
- Disability assessed using **Expanded Disability Status Scale (EDSS)**

CDP3M or CDP6M: confirmed disability progression at 3/6 months:
- **1-point increase in EDSS for baseline score of 3.0–5.0 or**
- **0.5-point increase for baseline score of 5.5–6.5**



1.6 Positioning of siponimod

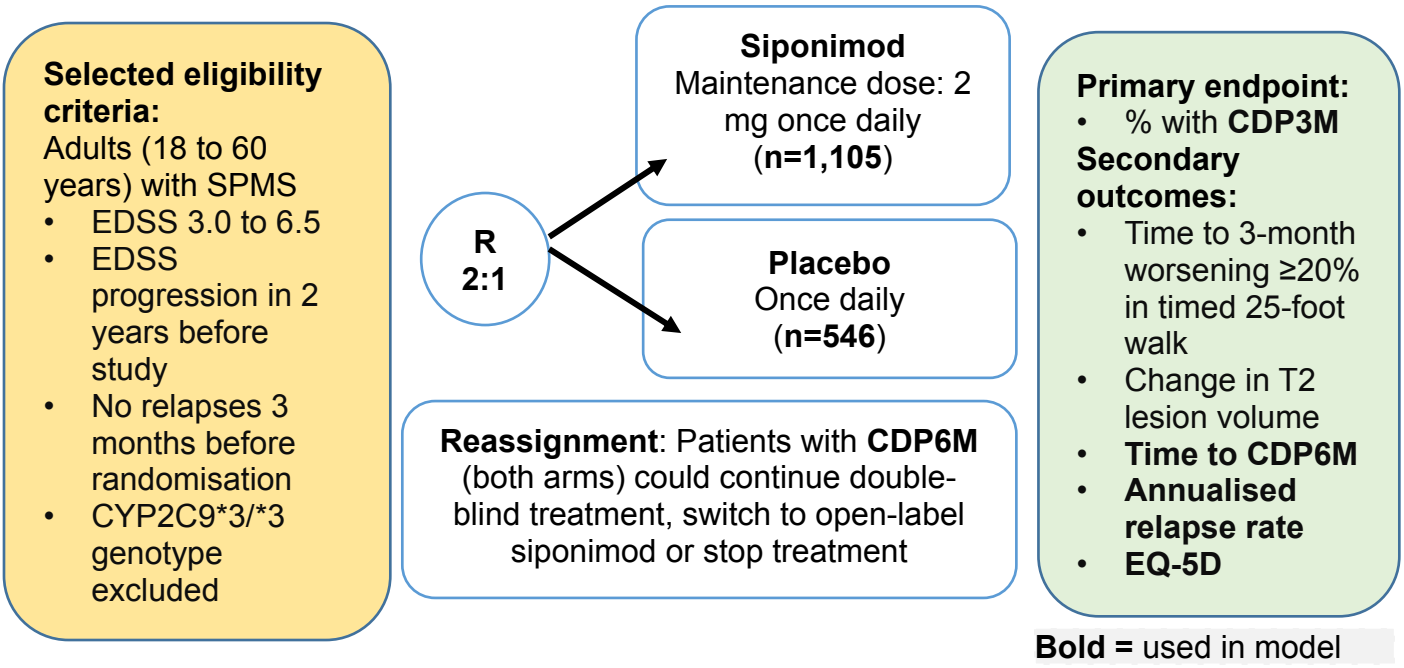


NHS England treatment algorithm stopping criteria for disease modifying therapies in relapsing-remitting MS:
- confirmed secondary progressive & **observable increase in disability for >12 months** without relapses
- SPMS usually only diagnosed when **EDSS ≥6.0** (except for active disease, could be lower)

NHS E treatment algorithm selected starting criteria for interferon beta-1b (Extavia), active secondary progressive:
- at least 2 disabling relapses in 2 years
- able to walk 10m or more (EDSS <7.0)
- minimal increase in disability due to progression over last 2 years

Company positioning: EDSS 3.0 to 6.5 (based on trial inclusion criteria), secondary progressive MS defined as **progressive increase in disability over 6 months**

1.7 EXPAND: double-blind, randomised, placebo-controlled, 10 UK sites



Bold = used in model

1.8 EXPAND baseline characteristics: Subgroup with active disease (relapses in 2 years prior to study or gadolinium-enhanced T1 lesions at baseline)

	Siponimod n=516	Placebo n=263
Age, mean years (SD)	[redacted]	[redacted]
Female (%)	[redacted]	[redacted]
Years since MS diagnosis, mean (SD)	[redacted]	[redacted]
Years since conversion to SPMS, mean (SD)	[redacted]	[redacted]
Number of relapses prior to screening		
Relapses in previous 2 years, mean (SD)	[redacted]	[redacted]
No relapses in previous 2 years	[redacted]	[redacted]
Relapses in previous year, mean (SD)	[redacted]	[redacted]
No relapses in previous year	[redacted]	[redacted]
EDSS, mean (SD)	[redacted]	[redacted]
≥1 Gadolinium-enhancing T1 lesions	[redacted]	[redacted]
Previous treatment with DMT, %	[redacted]	[redacted]

1.9 EXPAND: key results for active disease subgroup

	Siponimod n=516	Placebo n=263	Siponimod vs placebo	Siponimod vs placebo (full trial population)
% with 3-month confirmed disability progression	[redacted]	[redacted]	[redacted]	HR: 0.79 95% CI: 0.65 to 0.95 p=0.0134
% with 6-month confirmed disability progression	[redacted]	[redacted]	[redacted]	HR: 0.74 95% CI: 0.60 to 0.92 p=0.0058
Adjusted annualised relapse rate	[redacted]	[redacted]	[redacted]	ARR ratio: 0.45 95% CI: 0.34 to 0.59 p<0.0001

Data in **red box** used to inform efficacy estimates by matching adjusted indirect comparison used in model (see next section)

1.10 Indirect comparison – to compare with other treatments

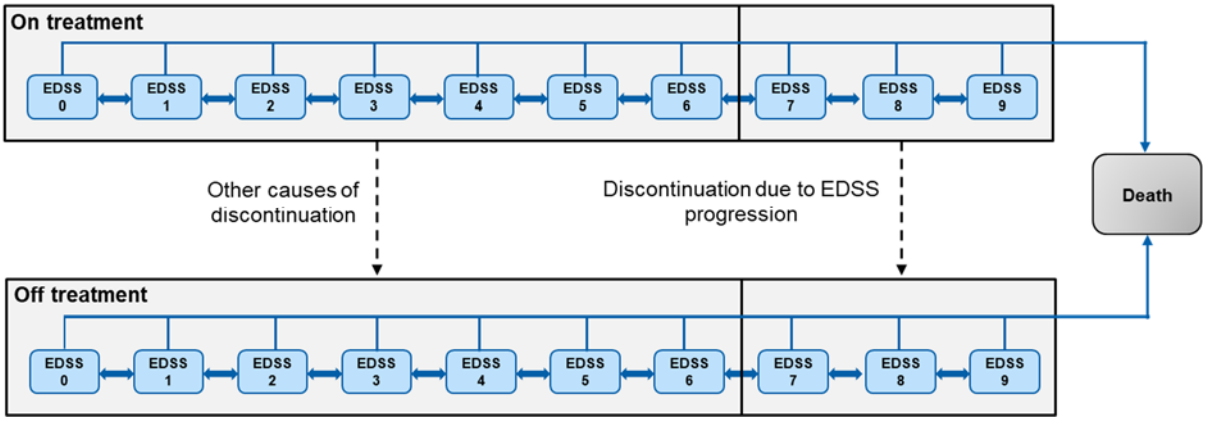
Company:

- Differences between comparator trials means network meta-analysis not feasible
- Instead matched individual patient data from EXPAND to aggregate data from comparator studies – a matching adjusted indirect comparison (MAIC)
- MAIC not feasible in the active subgroup; **using results for the full population preferable to unadjusted comparison**
- Results:
  - **Confirmed disability progression at 6 months:** HR=[redacted] vs. interferon beta-1b [redacted]
  - **Annualised relapse rates:** RR= [redacted] vs. interferon beta-1b [redacted]
- **Also results vs. other treatments used for relapsing-remitting MS. Not used in model. Company: comparison with interferon beta-1b more conservative**

ERG:

- MAIC has a small effective sample size, not matched for all important inclusion/ exclusion criteria
- Performed an exploratory network meta-analysis (NMA), also uses full trial populations
- Results:
  - **Confirmed disability progression at 6 months:** HR=0.80 vs. interferon beta-1b
  - **Annualised relapse rates:** RR=0.65 vs. interferon beta-1b

1.11 Company's model

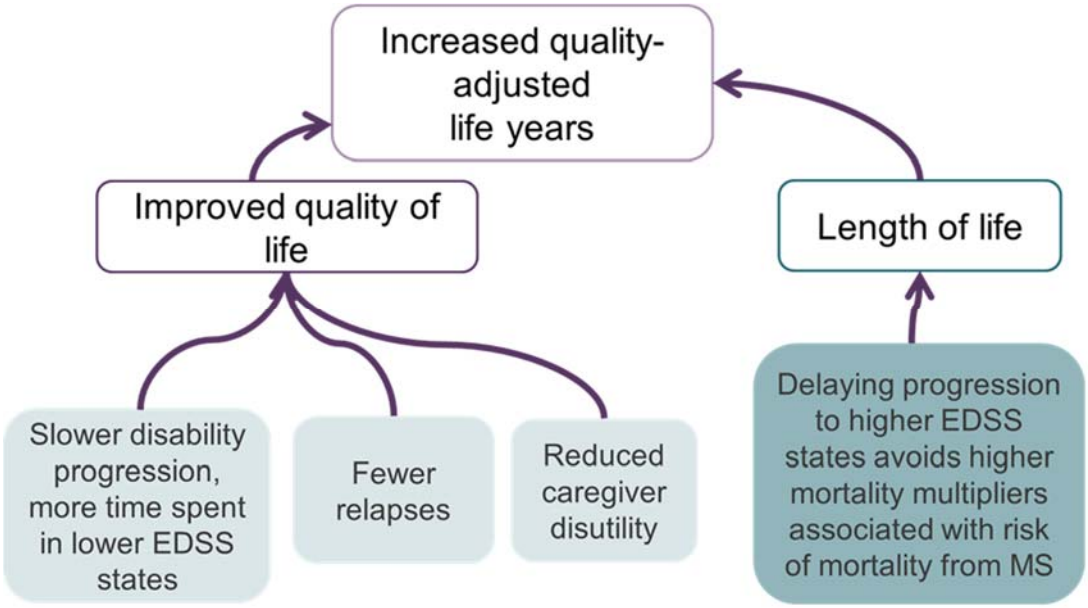


- Markov cohort model
- 10 EDSS health states (on/off treatment)
- Annual cycle, lifetime horizon
- Starting age 48 years; 40% men
- On-treatment effects (annualised relapse rates, disability progression, adverse events) from MAIC
- Treatment stops at EDSS ≥7
- After stopping treatment, patients follow natural disease course based on placebo arm of EXPAND and the London Ontario MS data set (preferred to British Columbia as has separate data for SPMS)
- **Analysis also run using baseline characteristics of active subgroup**

1.12 Key model assumptions

	Base-case assumption	Justification
Disability progression	Relapses have no residual effect on EDSS	Impact of relapses included through costs and disutility according to severity
	Treatment does not have impact on severity or duration of relapses	Little evidence, less frequent relapses in than in relapsing-remitting → impact on results negligible
	Transition probabilities: patients can move to lower EDSS states. **Treatment effect:** applied to EDSS progression but not regression	Some patients on placebo in EXPAND with EDSS <5 improved (moved to lower states) Company: conservative assumption, in line with previous appraisals
	After stopping treatment, patients follow the natural disease course	In line with previous appraisals
Treatment effect waning	Not applied. Company: all-cause discontinuation is proxy for waning	Company: consistent with TA533 where committee accepted discontinuation as a proxy for waning

1.13 Overview of how quality-adjusted life years accrue in the model



2. Summary of the draft technical report

2.1 In summary, the technical team considered the following:

Issue 1 Interferon beta-1b is likely to be the most appropriate comparator.

Issue 2 The baseline characteristics in EXPAND are generalisable to patients with active secondary progressive MS seen in the NHS.

Issue 3 Baseline characteristics of full trial population and active subgroup are similar; full trial population is a suitable proxy for the active subgroup. Both the company matching-adjusted indirect comparison and ERG exploratory network meta-analysis have limitations; both should be considered by the committee.

Issue 4 The treatment effect of siponimod is likely to diminish over time and scenarios should explore this.

Issue 5 The natural history data should be based on the placebo arm of EXPAND supplemented by the London Ontario registry data.

Issue 6 Treatment discontinuation should be extrapolated using an exponential distribution.

Issue 7 Health state utility values should be based on EQ-5D from EXPAND supplemented by data from Orme et al. (2007).

2.2 Taking these aspects into account where possible, the technical team's preferred assumptions result in incremental cost-effectiveness ratios (ICERs) of [redacted] per quality-adjusted life year (QALY) gained when the company's matching-adjusted indirect comparison is used and [redacted] per QALY gained when the ERG's network meta-analysis is used as the source of efficacy data (see table 3). These estimates do not account for a potential waning of treatment effect, which would increase the cost-effectiveness estimates.

2.3 The company considers the drug to be innovative, highlighting that some benefits such as improving cognitive processing speed and potentially disability regression and reduced relapse severity may not be captured in the QALY calculations. It also notes that it is administered orally. The technical team notes that there is already a treatment available for people with active secondary progressive MS. The committee will consider the innovative nature of siponimod.

2.4 One equality consideration was identified. Beta interferon-1b (Extavia) is the only treatment currently recommended for people with active secondary progressive MS. It is supplied as a solvent and powder which patients (or carers) must mix in order to take. This may be difficult for people with manual dexterity, visual or cognitive difficulties, which are common in people with multiple sclerosis. Some patients may find siponimod easier to take because it is administered orally. The committee will consider people who may find the preparation and administration of Extavia challenging when making its decision.

3. Key issues for consideration

Issue 1 – Positioning of siponimod in the treatment pathway

Background/description of issue	Many people progress to secondary progressive MS from relapsing-remitting MS. The **company** and **ERG** both indicate that there is a transition period where patients with relapsing-remitting MS may be suspected of having secondary progressive MS but are not formally diagnosed. This is especially the case for the population of interest in this appraisal, with active secondary progressive disease, since these patients may still have relapses. There is only one treatment option recommended by NICE for active secondary progressive MS, interferon beta-1b (Extavia), but during the transition period, some people with active secondary progressive MS may continue to have treatments licensed for relapsing-remitting MS. The **company** states that "research has revealed that clinicians believe that if a licensed and reimbursed disease modifying therapy were to become available for secondary progressive MS, this would reduce the hesitancy of identifying secondary progressive MS in patients." (company submission [CS], p20) Submissions from **clinical experts** note that "there is always a degree of clinical judgement which requires experience and subjectivity in the varying presentations of MS" but also that differences in opinion would be resolved by consensus.
Questions for engagement	a) What relapse and MRI criteria are used to diagnose active secondary progressive MS? Does this align with the definition of active secondary progressive MS used in the siponimod clinical trial of "relapses in 2 years prior to study or gadolinium-enhanced T1 lesions at baseline"? b) What proportion of patients are diagnosed with active secondary progressive MS without a prior diagnosis of relapsing-remitting MS? c) Would siponimod be used in the same position in the treatment pathway as interferon beta-1b (Extavia)?

	d) Would the availability of an additional treatment for active secondary progressive MS change the point at which active secondary progressive MS is diagnosed in clinical practice? e) Would siponimod displace therapies for relapsing-remitting MS used during the transition period in clinical practice?
Why this issue is important	The availability of an additional licensed treatment option for active secondary progressive MS may mean that there is a shorter transition period between relapsing-remitting and secondary progressive MS. Therefore, it would be less likely that people with secondary progressive MS would continue treatment with a disease modifying therapy licensed for relapsing-remitting MS used outside of its marketing authorisation. This would mean that these therapies are less relevant as comparators and that the main comparator is interferon beta-1b (Extavia).
Technical team preliminary scientific judgement and rationale	In order to considered for siponimod, a patient would need to have a confirmed diagnosis of secondary progressive MS. Therefore, if treatments licensed for relapsing-remitting MS are used while there is uncertainty about the diagnosis, this would no longer apply. Interferon beta-1b is likely to be the most appropriate comparator.

Issue 2 – Generalisability of the trial results to the NHS

Background/description of issue	The submission relies on a trial comparing siponimod to placebo (EXPAND), which enrolled participants across 31 countries, including the UK. See section 1.8 of the technical report for full baseline characteristics of the active disease population. The **company** states that the trial is expected to be generalisable to the secondary progressive MS population in NHS clinical practice (CS, p133). The **ERG** does not consider the company to have provided sufficient evidence of generalisability and note that there is potential geographic variation in outcomes and clinical practice across the countries in the trial (ERG report. p44).
Questions for engagement	a) Are the characteristics of participants in the EXPAND trial likely to reflect the characteristics of people with active secondary progressive MS seen in practice in the NHS?
Why this issue is important	If trial participants do not have similar characteristics to those who have active secondary progressive MS in the NHS, some of these factors may have an influence on how well the treatment works. That may mean that siponimod does not work as well in clinical practice as it did in the trials.
Technical team preliminary scientific judgement and rationale	The baseline characteristics in EXPAND appear broadly generalisable to patients in the NHS.

Issue 3 – Indirect treatment comparisons

Background/description of issue	The **company** identified 2 studies to indirectly compare the effectiveness of siponimod with interferon beta-1b (NA study, EU study), and 3 studies to compare with other treatments licensed for relapsing-remitting MS. The company concluded that although all the trials had a common comparator/anchor (placebo), there were differences in study design (duration, placebo administration), populations (inclusion/exclusion criteria, baseline characteristics), outcomes and outcome definitions. Therefore, it concluded a network meta-analysis (NMA) was not feasible and instead matched individual patient data from EXPAND to aggregate-level data from the other trials (that is, a matching adjusted indirect comparison, MAIC). The company stated that although the EU study included a subgroup with active disease, this was a narrower definition than in EXPAND. The NA study did not include an active subgroup, but the proportion of patients relapse-free and the mean number of relapses in the 2 years before the study differed by >10% compared with EXPAND. The company therefore conducted the MAIC using the full population from all studies, including EXPAND, despite having results for the active subgroup for the latter. The ERG compared the baseline characteristics of the full EXPAND population and the active subgroup and considered them to be comparable but were unable to make a formal comparison without individual patient level data. The Summary of Product Characteristics states the baseline characteristics of the subgroup with active disease were similar to the overall population. The **ERG** noted that the MAIC has a small effective sample size, not matched for all important inclusion/ exclusion criteria, and that not all relevant effect modifiers are included. The ERG considered that the baseline characteristics identified as effect modifiers by the company appear similar in the NA study and EXPAND, so the matching process which causes a significant reduction in sample size may not be justified. (Age, EDSS scores,

	duration of SPMS, number of relapses in prior 2 years, proportion female all appear similar). It therefore performed an exploratory NMA, which it used in its base case. This is also based on the full trial populations, not patients with active disease. The ERG noted that the company's MAIC results appeared to be optimistic, potentially overestimating the benefit of siponimod compared to interferon beta-1b • 6-month CDP: company MAIC hazard ratio (HR)=[redacted] ERG NMA HR=0.80 • Annualised relapse rate: company MAIC relative risk (RR)=[redacted] ERG NMA RR=0.65
Questions for engagement	a) Are the results for the full trial population generalisable to the active subgroup? b) Is the company's matching-adjusted indirect comparison or the ERG's exploratory network meta-analysis the most appropriate source of efficacy data for the model?
Why this issue is important	The efficacy estimates derived from the indirect treatment comparison is the main driver of cost effectiveness. The results of the model are sensitive to the efficacy parameters so any uncertainty in the suitability of the full trial population as a proxy for the active secondary progressive MS subgroup will lead to uncertainty in the cost-effectiveness results. However, the hazard ratio vs. placebo for 6-month confirmed disability progression in the full EXPAND population is 0.74, compared with [redacted] in the active subgroup. This is likely because people with active disease derive more benefit from siponimod. This suggests that using the full trial population may be less favourable to siponimod. (The annualised relapse rate is lower in the full trial population, 0.45 vs. [redacted] but this is not as important in the model as disability)
Technical team preliminary scientific judgement and rationale	The technical team considers that the baseline characteristics of the full EXPAND population and active subgroup are broadly similar and that the full trial population is a suitable proxy for the active subgroup. This assumption may underestimate the efficacy of siponimod in the active subgroup, however the magnitude of any underestimation is unclear and may be outweighed by uncertainties in the indirect comparison. Both the company's and ERG's approaches are subject to uncertainty. The company's approach means that the effective sample size used to generate the effectiveness estimates is small. The ERG's approach is also uncertain because of the heterogeneity between the trials.

Issue 4 – Extrapolating the effects of treatment beyond the follow up period in the clinical trials

Background/description of issue	The efficacy of siponimod may reduce over time, but some patients may continue taking it, especially if the stopping criteria for treatments for active secondary progressive MS in the NHS England treatment algorithm (section 13) are not met: • No reduction in frequency or severity of relapses compared with pre-treatment phase following a minimum 6-month period of treatment • Intolerable adverse effects of the drug • Development of inability to walk persistent for more than 6 months, unless unable to walk for reasons other than MS The **company** models a stopping rule at EDSS >7.0 to reflect the 3rd bullet of the NHS England criteria. It states that all-cause discontinuation is a suitable proxy for treatment effect waning, and that this assumption was accepted in NICE TA533, ocrelizumab for treating relapsing-remitting MS. The **technical team** notes that TA533 states "The committee considered that a large proportion of patients who stop treatment are likely to do so because treatment effectiveness reduces over time and as the disease progresses […] stopping treatment could be a proxy for waning, but that some patients having ocrelizumab may continue treatment despite a waning effect if there are no better treatment options. […] It recognised that these factors meant that, in the economic model, the difference in waning of effect between treatments may have been underestimated." TA533 differs to the current appraisal because there are several subsequent treatment options available for relapsing-remitting MS, whereas people with active secondary progressive MS who stop siponimod will either be treated with interferon beta-1b or best supportive care. In addition, in TA533 the company supported its argument that the treatment effect does not wane by providing 4 year follow-up data showing no waning in the frequency of relapses. Similar data are not currently available for siponimod. Therefore, using all-cause discontinuation as a proxy for treatment effect waning may not fully account for diminishing efficacy.

Questions for engagement	a) Would the efficacy of siponimod be expected to diminish over time? b) Would patients (who do not meet the stopping criteria described in the NHS England treatment algorithm) continue to be treated with siponimod if treatment efficacy reduces over time?
Why this issue is important	Because the efficacy of siponimod is the main driver of the cost-effectiveness results assumptions about long-term treatment efficacy have a substantial effect on the results. If people to continue to incur the costs of treatment but receive less benefit from it, this may not be a cost-effective use of resources
Technical team preliminary scientific judgement and rationale	The company's assumption may be plausible but because there is only 1 other treatment recommended by NICE for active secondary progressive MS some patients may continue to have siponimod even if efficacy is less than expected. The technical team would prefer to see analyses in line with previous appraisals in relapsing-remitting MS, for example where the treatment effect is modelled as decreasing by 50% after 5 years, or where it reduces by 25% after 2 years and 50% after 5 years. Estimates of long-term efficacy in the comparator arm should be based on clinical data were available, if unavailable the same assumptions should be applied for both siponimod and the comparator.

Issue 5 – Source of natural history data

Background/description of issue	The company derived the transition probabilities between EDSS health states to model the natural history of the disease (that is, in the absence of siponimod) from data for the placebo group of EXPAND supplemented with data from the London Ontario registry. Using this approach resulted in people being able to regress (improve) to less severe EDSS states. In line with other MS appraisals, no treatment effect is applied to EDSS regression in the model. The ERG, in discussion with its clinical adviser highlighted that over the long-term, people with secondary progressive MS will progress to (or sometimes plateau at) higher EDSS states, but in the short-term, if people have a relapse from which they recover they could improve before they worsen again. The ERG assume that this short timeframe may be approximately 2-3 months, and point out that as transitions in the model are yearly, regressions are likely to be very rare. Previous MS appraisals have used the London Ontario natural history dataset, which does not allow improvements in EDSS. The ERG considers the London Ontario data set to be more appropriate then the trial data because these data were collected over 25 years compared with the 2-year duration of the EXPAND trial.
Questions for engagement	a) Is it appropriate for the model to include the possibility that during the natural course of secondary progressive MS patients may improve EDSS state?
Why this issue is important	The data informing the normal course of disease progression is a fundamental part of the model structure. In isolation, the effect of choice of dataset on the cost effectiveness estimate appears small, but it may be larger when combined with other changes.
Technical team preliminary scientific judgement and rationale	The company's base case transition probabilities using EXPAND supplemented by data from London Ontario are appropriate, as this more closely reflects the outcomes observed in the trial.

Issue 6 – Treatment discontinuation

Background/description of issue	In addition to everyone stopping treatment at EDSS >7.0, the company models treatment discontinuation by fitting fully parametric curves to the discontinuation time-to-event information obtained from the treatment group in the EXPAND trial. The company suggests that this accounts for people stopping treatment due to an adverse event or lack of effectiveness (see issue 4). The choice of parametric fit was based on visual inspection and assessing statistics about how well the curves fit the observed data. According to these criteria, the exponential and Weibull distributions were considered the most appropriate. The company chose the Weibull distribution, as the exponential showed a high number of people remaining on treatment beyond the trial duration. The ERG considered the exponential distribution to be equally plausible and a better statistical fit. In the first 7 years slightly more people stay on siponimod using the exponential distribution, whereas slightly fewer stay on siponimod after 7 years compared with the exponential distribution.
Questions for engagement	a) Which of the estimates of the number of patients remaining on treatment is more plausible?
Why this issue is important	The more people that continue taking siponimod, the higher the costs of treatment, but also the potential benefits. The ERG analyses suggest using the exponential instead of the Weibull has a small effect on the cost effectiveness estimates.
Technical team preliminary scientific judgement and rationale	The technical team prefers the exponential parametric curve fitted to discontinuation data as per ERG base-case – the long-term continuation estimates for the exponential and Weibull extrapolations appear equally plausible but the exponential has a better statistical fit.

Issue 7 – Utility values

<table>
<tr><td>Background/description of issue</td><td>The company used utility values from EXPAND (EQ-5D 3L) supplemented with values from Orme et al (2007) for EDSS states 0,1,2,8 and 9 because there were few people with these EDSS values in the trial.
The ERG note that there is considerable uncertainty about the EQ-5D values and they might not be generalisable. The ERG prefers the Orme data because it is based on more patients.
The technical team notes that the utility value for EDSS 3 is lower (0.529) than EDSS 4 (0.565) in the Orme data, which may lack face validity.
<table>
<tr><th>EDSS</th><th>Company: EXPAND and Orme et al.</th><th>Orme et al.</th></tr>
<tr><td>0</td><td>0.825</td><td>0.825</td></tr>
<tr><td>1</td><td>0.754</td><td>0.754</td></tr>
<tr><td>2</td><td>0.660</td><td>0.660</td></tr>
<tr><td>3</td><td>[redacted]</td><td>0.529</td></tr>
<tr><td>4</td><td>[redacted]</td><td>0.565</td></tr>
<tr><td>5</td><td>[redacted]</td><td>0.473</td></tr>
<tr><td>6</td><td>[redacted]</td><td>0.413</td></tr>
<tr><td>7</td><td>[redacted]</td><td>0.252</td></tr>
<tr><td>8</td><td>-0.094</td><td>-0.094</td></tr>
<tr><td>9</td><td>-0.240</td><td>-0.240</td></tr>
</table>
</td></tr>
<tr><td>Questions for engagement</td><td>a) Which health state utility values are more plausible? EXPAND supplemented by Orme et al. or Orme et al. alone?</td></tr>
<tr><td>Why this issue is important</td><td>Using the trial utility values means that patients in EDSS states 3-7 have a higher utility than if Orme is used. This will benefit siponimod if it enables more people to stay in these states.</td></tr>
<tr><td>Technical team preliminary scientific judgement and rationale</td><td>The technical team prefers the company’s health state utility values from EXPAND supplemented by data from Orme et al – the EXPAND trial is likely to be generalisable to patients in the NHS, and is more contemporary than Orme et al.</td></tr>
</table>

4. Issues for information

Tables 1 and 2 are provided to stakeholders for information only and not included in the Technical Report comments table.

Table 1: Technical team preferred assumptions and impact on the cost-effectiveness estimate.

Active subgroup vs. interferon beta-1b, as this is the most appropriate comparator (see issue 1)				
Alteration	**Technical team rationale**	**Inc costs**	**Inc QALYs**	**ICER**
Company deterministic base case (efficacy from MAIC)	**–**	[redacted]	1.35	[redacted]
ERG deterministic base case (efficacy from NMA)	Includes several technical team preferred assumptions, including the exponential for discontinuation (issue 6) see also table 2.	[redacted]	0.72	[redacted]
1. ERG base case + assumption that efficacy of siponimod decreases over time	Siponimod may become less effective over time. Discontinuation not a proxy if people continue because of a lack of alternatives.			Unknown[a]
2. ERG base case + transition matrix based on EXPAND supplemented by data from the London Ontario registry	Trial data is more recent than the registry. As transitions to lower EDSS states observed in the trial, appropriate to model.	[redacted]	0.93	[redacted]
3. ERG base case + health state utilities from EXPAND supplemented by Orme	Preferable to use data from the trial which is considered generalisable to NHS.	[redacted]	0.86	[redacted]
Technical team's preferred assumptions: ERG base case + 1-3, efficacy from ERG NMA	**–**	[redacted]	1.06	[redacted]
Technical team's preferred assumptions: ERG base case + 1-3, efficacy from company MAIC	**–**	[redacted]	1.67	[redacted]
Scenario: ERG base case with MAIC	**-**	[redacted]	1.15	[redacted]

[a] Where the ICER is unknown the technical team was unable to implement their preferred assumption within the current model structure

Table 2: Other issues for information

Issue	Comments
Input parameters	The ERG made several changes in their base case, which the technical team considers appropriate. They have a minimal impact on the cost-effectiveness results: • Treatment effect for siponimod vs. interferon beta-1b applied as a rate instead of a probability • Costs of £35 for genotyping borne by company (company model assumes NHS) • Health state management costs obtained from TA320 • Correcting the cost for relapses in the model to match the value in the company submission
Innovation	The company considers siponimod to be innovative. It notes that there are additional benefits not captured within the QALY calculation. These include: improving cognitive processing speed, disability regression and reduced relapse severity, which are not modelled in the economic analysis. It also notes that siponimod is administered orally, therefore avoiding the administration requirements of infusions or injections, and providing greater convenience to patients. The technical team notes that there is already a treatment available for people with active secondary progressive MS. The committee will consider the innovative nature of siponimod.
Equality considerations	Beta interferon-1b (Extavia) is the only treatment currently recommended for people with active secondary progressive MS. NICE technology appraisal guidance 527 for relapsing-remitting MS states that "interferon beta-1b is supplied as a solvent and powder, which patients (or carers) must mix each time they administer the treatment. This process is more difficult than treatments employing ready-to-use injection devices. The committee understood that some people will therefore have difficulty using Extavia [and Betaferon], particularly people with manual dexterity, visual or cognitive difficulties, which are common in people with multiple sclerosis. The committee concluded that consideration should be given to this group of people with respect to the ease of preparation and administration of beta interferons." Some patients may find siponimod easier to take because it is administered orally. The committee will consider the group of people who may find preparing and administering Extavia challenging when making its decision.

Authors

Amanda Adler

Appraisal committee chair

Alan Lamb

Technical lead

Ross Dent

Technical adviser

Nicole Elliott

Associate director

With input from the lead team:

Mark Glover

Lead team member

Nick Latimer

Lead team member

Nigel Westwood

Lead team member

NICE National Institute for Health and Care Excellence

Technical engagement response form

Siponimod for treating secondary progressive multiple sclerosis [ID1304]

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholders responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments **Monday 10 February 2020**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- 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.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. 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.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- 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 [redacted], all information submitted under [redacted], and all information submitted

under [redacted] in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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 past or current, direct or indirect links to, or funding from, the tobacco industry.	None

Questions for engagement

Issue 1: Positioning of siponimod in the treatment pathway	
a) What relapse and MRI criteria are used to diagnose active secondary progressive MS? Does this align with the definition of active secondary progressive MS used in the siponimod clinical trial of "relapses in 2 years prior to study or gadolinium-enhanced T1 lesions at baseline"?	In the EXPAND trial, the Active secondary progressive multiple sclerosis (SPMS) subgroup reflects the available relevant baseline characteristics from the trial: patients who experienced relapses in the two years prior to the study and/or who had gadolinium-enhanced T1 lesions at baseline. Clinical experts in the reappraisal of cladribine for relapsing-remitting multiple sclerosis (RRMS) (TA616) highlighted that the criteria for MRI evidence of disease activity used in marketing authorisations are difficult to use in clinical practice because there is a spectrum of disease activity rather than rigidly defined stages.[1] They highlighted how an increase in the number of T2 lesions is also an important indicator of disease activity, which has been reflected in the updated NICE guidance, however, as an increase in T2 lesions over the preceding year was not a baseline characteristic that was recorded in the EXPAND trial, it is not possible to formally incorporate it into the definition used for subgroup analysis. Novartis believes that the results from the specific subgroup definition used in the analysis are generalisable to the population of "active disease evidenced by relapses or imaging features". Indeed, this subgroup analysis underpinned the European Medicine Agency's (EMA) consideration of the final licensed indication. The Clinical Experts present on the Technical Engagement call with NICE on 23rd January agreed that this subgroup analysis of the trial was generalisable to UK clinical practice.
b) What proportion of patients are diagnosed with active secondary progressive MS without a prior diagnosis of relapsing-remitting MS?	Novartis understands this proportion of patients to be very small. Around 85% of MS patients are first diagnosed with RRMS, with the remaining 10–15% of patients diagnosed with primary-progressive multiple sclerosis (PPMS).[2] A very small number of people may be diagnosed with SPMS from the outset, but this is most likely in cases where previous relapses went undiagnosed or occurred at a time prior to wide availability of effective disease-modifying therapies (DMTs).

c) Would siponimod be used in the same position in the treatment pathway as interferon beta-1b (Extavia)?	Yes. As the only licensed and NICE-recommended treatment option for treating SPMS with active disease (evidenced by relapses), we agree with the technical team that siponimod would be positioned in the treatment pathway in the same way as interferon beta-1b (Extavia).
d) Would the availability of an additional treatment for active secondary progressive MS change the point at which active secondary progressive MS is diagnosed in clinical practice?	Yes. As discussed in the company submission (CS) Document B Section B.1.3, clinicians have reported that due to uncertainty around the transition from RRMS to SPMS, and the limited options for treatment once diagnosed with SPMS, they avoid identifying SPMS for as long as is clinically possible, and RRMS DMTs are continued in the transition period.[3-5] The introduction of siponimod may result in a step-change in earlier identification of the transition to SPMS by reducing the hesitancy of formally identifying active SPMS.
e) Would siponimod displace therapies for relapsing-remitting MS used during the transition period in clinical practice?	This is a possibility. We agree with the technical team's conclusion that interferon beta-1b (Extavia) is the most appropriate comparator. As the only licensed and NICE-recommended treatment option for treating SPMS with active disease (evidenced by relapses), interferon beta-1b (Extavia) should be considered as the base case comparator. However, as was discussed during the Technical Engagement call on 23rd January, it is possible that siponimod may also displace therapies for RRMS used outside of their marketing authorisation during the transition period to SPMS. Analyses of comparative clinical effectiveness and cost-effectiveness vs. other DMTs that could potentially be displaced were included in our submission for completeness. However, none of these DMTs are indicated for use in SPMS.
Issue 2: Generalisability of the trial results to the NHS	
a) Are the characteristics of participants in the EXPAND trial likely to reflect the characteristics of people with active secondary progressive MS seen in practice in the NHS?	Yes. As described in Section B.2.9.4 of the CS Document B, the EXPAND trial can be generalised to a recognisable English SPMS population in the following ways: • MS is usually diagnosed when patients are in their 20s–30s and later transition to the less inflammatory and more neurodegenerative SPMS phase. The patients in EXPAND had a mean age of 48 years, in line with this later transition, and most patients were female (60.1%), reflective of the fact that multiple sclerosis (MS) is more common in women than men.[6]

	• The EXPAND study population is relevant to the epidemiology of SPMS in the UK and included patients from ten clinical trial sites across the UK. The majority of the study population were [redacted] which is in line with the majority White population in the UK (86.0%).[7] • Most healthcare professionals (HCPs) do not use a standardised method to diagnose SPMS, however in a survey of UK based health-care professionals, the majority (60%, n=59) diagnosed SPMS between Expanded Disability Status Scale (EDSS) 5.5 and 6.5.[8] Patients in the EXPAND trial had a median EDSS of 6.0, reflective of standard UK clinical practice. Novartis believes the characteristics of the EXPAND trial population, and specifically the Active SPMS subgroup are generalisable to the Active SPMS population in the NHS in England. The Clinical Experts on the Technical Engagement call agreed that the EXPAND population is generalisable to SPMS patients in UK clinical practice.
Issue 3: Indirect treatment comparisons	
a) Are the results for the EXPAND full trial population generalisable to the active subgroup?	No, the efficacy results in the Active SPMS subgroup are meaningfully better than those in the full SPMS population. Where Active subgroup data can be used, they should be. However, it is important to note that the matching adjusted indirect comparison (MAIC), which cannot use active SPMS subgroup data because of the need to match to the comparator trial populations, does produce results that are more generalisable to an Active SPMS population that the intention-to-treat (ITT) population before matching and adjusting. The characteristics of the unadjusted ITT population of the EXPAND trial do not accurately reflect the Active SPMS subgroup: the numbers of relapses and Gd+ lesions at baseline are markedly different between the ITT and Active SPMS subgroup, and these factors are known to be treatment effect modifiers (see section B2.9.2 of the CS Document B). The Active SPMS data should be used wherever possible as the use of full SPMS data will underestimate the efficacy of siponimod in the Active SPMS subgroup and would not accurately reflect the population who would be treated with siponimod in clinical practice.

Notably, in the base case indirect comparison to interferon beta-1b (Extavia), imbalances in treatment effect modifiers were identified between the EXPAND and comparator trials, necessitating a MAIC which was not possible in the subgroup alone. Nonetheless the *unadjusted* full trial population is not used as the results of the matching and adjusting process required in the MAIC analysis were selective for a more active subset of the EXPAND trial: average age and baseline EDSS are lowered, and the average number of relapses per patient in the two years prior to the trial is increased (Table 1).

Novartis considers that although the extrapolation of the MAIC results to the Active SPMS subgroup has inherent limitations, it remains preferable to an unadjusted naïve comparison of data between two trials which are known to differ in treatment effect modifiers.

Table 1: Results of population matching and adjustment for 6-month CDP – siponimod vs. interferon beta-1b 250 µg Q2D

Variables	North American Study	EXPAND (unmatched)	EXPAND (matched and unadjusted)	EXPAND (matched and adjusted)
N (N_{eff})	939	[redacted]	[redacted]	[redacted]
Age (mean years [SD])	46.83 (8.14)	[redacted]	[redacted]	[redacted]
EDSS score at screening (mean [SD])	5.13 (1.18)	[redacted]	[redacted]	[redacted]
MS duration since diagnosis (mean years [SD])	14.66 (8.32)	[redacted]	[redacted]	[redacted]
Duration of SPMS (mean years [SD])	4.03 (3.48)	[redacted]	[redacted]	[redacted]

	Number of relapses in prior 2 years (mean [SD])	0.83 (1.32)	[redacted]	[redacted]	[redacted]
	Sex (proportion female)	62.6%	[redacted]	[redacted]	[redacted]

Matched sample excludes patients >55 years old, EDSS <3 or >6.5, and those with prior IFN-beta therapy.
Abbreviations: CDP: confirmed disability progression; EDSS: expanded disability status scale; MS: multiple sclerosis; N_{eff}: effective sample size; Q2D: every other day; SD: standard deviation; SPMS: secondary progressive multiple sclerosis.

b) Is the company's matching-adjusted indirect comparison or the ERG's exploratory network meta-analysis the most appropriate source of efficacy data for the model?

We believe that the Novartis MAIC is the most appropriate source of efficacy data for the model as it is the only method that addresses the substantial heterogeneity between the clinical studies of siponimod and interferon beta-1b.

As described in Section B.2.9 of the CS Document B, following the guidance of the NICE Decision Support Unit (DSU) Technical Support Document (TSD) 18, a feasibility assessment of conducting indirect treatment comparisons (ITCs) for siponimod compared with other DMTs was performed. This assessment focussed on determining if treatment effect modifiers are present and if there is an imbalance between the trial populations.

Significant heterogeneity was observed across the identified trials in SPMS, leading to a standard network meta-analysis (NMA) approach being deemed infeasible. The presence of significant clinical heterogeneity, inconsistency and dissimilarity, as well as an imbalance of effect modifiers between EXPAND and each of the comparator trials undermines the validity of ITC methods that are based on summary-level data, such as an NMA. Failure to account for differences in trial designs and effect modifiers between trial populations can lead to misleading comparisons of treatment effect, significant bias and clinically implausible results as a result of differences in the prognosis and treatment effect within disparate patient populations.

This heterogeneity can be observed most notably when considering the North American and European studies. Both studies investigated exactly the same intervention and comparator (interferon beta-1b vs placebo) but resulted in different outcomes; while the European study met its primary endpoint for disability progression, the North American study did not. The European study included a much younger population who had had SPMS for a much shorter time. These imbalances in the treatment effect

	modifiers resulted in significantly different trial results and highlight the need for adjustment when comparing across the SPMS trials. The matching and adjusting processes of the MAIC analysis result in a reduced sample size for each comparison. For the MAIC between EXPAND and the North American study – the only study reporting 6-month confirmed disability progression (CDP) for interferon beta-1b – the EXPAND population was reduced from [redacted] when unmatched to an effective sample size of [redacted] when fully matched and adjusted. This still provides a large sample size for analysis, however the relative reduction of [redacted] demonstrates the large imbalance in population characteristics which modify treatment effect between the two trials. Following the guidance of the NICE DSU TSD18, the requirements for an NMA are not met and anchored MAICs are the most appropriate and robust comparative method because the majority of important clinical differences between the trials could be adjusted for using MAIC methodology through use of individual patient data (IPD) from EXPAND. Despite the caveat that not all differences could be accounted for, MAIC still provides the most appropriate method for indirect comparison. If an unadjusted NMA were to be considered by the Appraisal Committee as an alternative scenario, the NMA should utilise the data from the *post hoc* Active SPMS subgroup rather than the full SPMS ITT population that was used in the Evidence Review Group's (ERG) exploratory NMA. This is because these data reflect the license for siponimod and most closely reflect the population that would be treated in NHS clinical practice. Unlike in the MAIC analysis, where the ITT population is a suitable source of data, as the adjustment processes result in a more active population set (see response to Q3a), the lack of adjustment in the NMA approach makes the ITT population inappropriate to be used. As such, Novartis has prepared and provided an alternative NMA as additional evidence to this response, using the Active SPMS subgroup data (Appendix A). However, although an NMA based on the Active SPMS subgroup data is more representative than one based on the ITT data, due to the reasons outlined above and in CS Document B surrounding the heterogeneity of the trials, the use of an NMA at all is still inferior to a MAIC analysis. As noted on the Technical Engagement call, the data used in the model by the Technical Team in their "efficacy from NMA" analyses presented in table 1 of the Technical Report are in fact a naïve comparison of the Active subgroup of EXPAND with the North American study (see non-MAIC model inputs, worksheet 'Efficacy', cells F35:F46 for 6-month CDP,

	F50:F61 for 3-month CDP and F84:F95 for annualised relapse rate [ARR]). These figures (treatment vs placebo) are the same as those from the alternative NMA provided as additional evidence (Appendix A) because they utilise the same comparative trial data and there are no closed loops of evidence in the trial network that would result in adjustments to the trial estimates.
Issue 4: Extrapolating the effects of treatment beyond the follow up period in the clinical trials	
a) Would the efficacy of siponimod be expected to diminish over time?	No. There is no clinical evidence to suggest that the treatment effect of siponimod reduces over time. With respect to data to support lack of waning in TA533 for ocrelizumab, the Technical Report stated that "Similar data are not currently available for siponimod". However this is not the case, as described in Section B.2.6.8, page 55 of the CS Document B, there are data available demonstrating continued, and slightly improved, efficacy estimates for time to 6-month CDP up to 5.5 years, compared with efficacy results from the core-study duration (median 18 months) for siponimod compared with placebo. Since our submission to NICE, further analyses explore continued treatment efficacy up to 6 years (72 months) of treatment. These additional data are supplied in the accompanying Appendix B and show evidence that treatment effect has been observed to be maintained for siponimod up to 72 months after treatment initiation. Treating neurologists at a Novartis-organised health technology assessment (HTA) advisory board agreed that including treatment waning for siponimod would be inappropriate. They considered that for antibody-based treatments, a high percentage of patients may have neutralising antibodies and a waning effect can be seen in those cases, but as siponimod is a small molecule rather than antibody-based therapy, treatment waning is not expected. Furthermore, during the Technical Engagement call, one of the Clinical Experts noted that siponimod may have a different mechanism of action to other DMTs, and as such it may not be appropriate to apply the same waning assumptions as have been applied to therapies for RRMS. The Expert also noted that patients with SPMS may remain on treatment for cognitive benefits which are not captured by EDSS and are therefore not considered or valued in the economic analysis; a consequence of this is that applying an arbitrary waning of efficacy on EDSS alone will further bias the model away from the incremental cost-effectiveness ratio (ICER) that would result if cognitive benefits were able to be

	captured in the model. Appendix B provides additional long-term evidence from the EXPAND trial, which demonstrates a continued reduced risk of cognitive worsening on symbol digit modalities test (SDMT) up to 5 years after treatment initiation (compared to 24 months in the CS Document B). Considering the clinical expert opinion, and the clinical evidence from the extension phase of the EXPAND trial, which demonstrates maintenance of treatment effect up to 6 years, it would be inappropriate to assume there would be a sudden, significant loss of efficacy beyond 6 years. Instead, all-cause discontinuation, as considered in our economic model, captures patients withdrawing treatment due to adverse events (AEs) or lack of effectiveness, thus already incorporating the effect of any potential treatment waning. The use of all-cause discontinuation as a proxy for treatment waning is consistent with the approach preferred by the committee in the NICE appraisal for ocrelizumab in RRMS (TA533).[10] We do not support the validity of the NICE technical team's suggestion to see analyses of efficacy decreasing for siponimod by 50% after 5 years or 25% after 2 years and 50% after 5 years. However, having reflected on Technical Engagement discussions, we have, as requested by the NICE technical team, provided alongside this response document an updated version of the economic model incorporating exploratory treatment waning scenarios. These scenarios take into account the long-term follow up data for siponimod and precedent in a relevant MS appraisal for the main comparator; results are presented in the accompanying Appendix B to allow the Committee to explore uncertainty in the long-term treatment effect of siponimod.
b) Would patients (who do not meet the stopping criteria described in the NHS England treatment algorithm) continue to be treated with siponimod if treatment efficacy reduces over time?	No. If it were considered that a treatment was no longer working for a patient, it would be reasonable to assume that they would be withdrawn from treatment. Loss of efficacy of a treatment for patients with SPMS may also result in progression of their disability, which, given their high starting EDSS (median 6.0 in EXPAND) would bring them very close to an EDSS of 7.0, at which point they would be discontinued from treatment in any case under the NHS England MS DMT algorithm. As described above, on the Technical Engagement call one of the Clinical Experts noted that if a patient was benefiting from treatment in ways that are not captured by EDSS or relapse, such as cognitive and/or upper limb benefits, such treatment may be continued even in the presence of EDSS

	worsening. However, as any non-EDSS and non-relapse benefits are not considered in the economic analysis, the ICER is already conservative and any imposition of arbitrary waning assumptions based purely on EDSS would worsen such bias. Clinical Expert opinion is consistent with the Novartis base case, which remains that patients no longer benefiting from DMTs would discontinue treatment.
Issue 5: Source of natural history data	
a) Is it appropriate for the model to include the possibility that during the natural course of secondary progressive MS patients may improve EDSS state?	Yes. We agree with the technical team's conclusion that using EXPAND supplemented by data from London Ontario is the most appropriate source for the base case transition probabilities, which includes the possibility that patients may improve EDSS state during the natural course of SPMS. The EXPAND trial placebo-arm data provides the most recent data source for patients with SPMS. The London Ontario dataset is well established and has been used extensively in previous NICE MS submissions.[10] It also provides separate natural history transitions for RRMS and SPMS. However, it does not as accurately reflect the outcomes observed in the EXPAND trial. In the EXPAND trial, it was observed that some patients with SPMS receiving placebo experienced disability regression (i.e. moved to lower EDSS states). The model therefore should allow both disability progression and regression to accurately reflect the observations of the trial. The ERG's preferred source (London Ontario data only) was previously found to contain retrospectively smoothed disability data (rather than actual, real-time collected disability scores), censoring any improvement in EDSS.[12] The London Ontario data set does not suggest improvements do not occur, but simply does not allow them. As a conservative assumption, the treatment effect of DMTs is applied only to EDSS progression but not to EDSS regression, in line with all previous NICE appraisals.
Issue 6: Treatment discontinuation	
a) Which of the estimates of the number of patients remaining on treatment is more plausible?	The ERG has been inconsistent in their choice for modelling treatment discontinuation. They stated a preference for the exponential distribution over Weibull, however they utilised a time-constant model rather than a time-dependent approach. This approach therefore does not utilise the exponential distribution at all, but instead uses a distribution that gives unrealistically high proportions of patients

remaining on treatment at 10, 15 and 20 years (Table 2). Time-constant discontinuation was considered unrealistic by treating neurologists at Novartis-organised advisory boards; this is clearly evident from examination of the data at later time-points in Table 2.

We also note, as raised during the Technical Engagement call, that the technical team have applied time-constant discontinuation in error rather than their preference for exponential distribution-based time-dependent discontinuation in their analyses as a result of the ERG model base case.

Discontinuation rates in the company submission were based on a time-dependent model and were obtained from the EXPAND trial, which was the primary source of data on all-cause discontinuation of treatment. Different distributions were fitted to the data to estimate the proportion of patients who discontinued beyond the trial duration. We agree with the technical team that, based on the model fit, the Akaike information criterion (AIC) statistic and visual inspection, the exponential and Weibull functions are the most appropriate fit to the data. Table 2 shows a five-yearly landmark analysis of discontinuation using the Weibull, exponential, and time-constant approaches; We accept the technical team's preference for use of the exponential distribution in the revised base case (presented in Table 2 of Appendix B submitted with this response).

Table 2: Proportion of patients remaining on treatment using different treatment discontinuation models

Cycle	Proportion of patients on treatment (%)		
	Time-dependent Weibull	Time-dependent Exponential	Time-constant
0	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]
20	[redacted]	[redacted]	[redacted]
25	[redacted]	[redacted]	[redacted]

	30	[redacted]	[redacted]	[redacted]
	35	[redacted]	[redacted]	[redacted]
	40	[redacted]	[redacted]	[redacted]
	45	[redacted]	[redacted]	[redacted]
	50	[redacted]	[redacted]	[redacted]
Issue 7: Utility values				
a) Which health state utility values are more plausible? EXPAND supplemented by Orme et al. or Orme et al. alone?	We agree with the NICE technical team that the EXPAND plus Orme utilities are more plausible than utilities from Orme et al alone. Novartis agrees with the technical team that the Orme data may lack face validity as the utility value for EDSS 3 is lower (0.529) than EDSS 4 (0.565) which suggests lower quality of life in less disabled patients (this is not the case for the EXPAND data utilities). Novartis agrees that the EXPAND trial is generalisable to patients in the NHS, and is more contemporary than Orme et al.			

References

1. National Institute for Health and Clinical Excellence (NICE). Cladribine for treating relapsing-remitting multiple sclerosis. Technology appraisal guidance [TA616]. https://www.nice.org.uk/guidance/ta616. Accessed 23-Jan-2020.
2. Multiple Sclerosis Trust. Types of MS. https://www.mstrust.org.uk/about-ms/what-ms/types-ms. Accessed 05-Mar-2019.
3. Novartis Data on File (Caseby SCL; Montgomery SM; Woodhouse FA; Kroes MK). [Manuscript under development] Transition to secondary progressive multiple sclerosis: the consequences for patients and healthcare systems, a healthcare professional survey 2019.
4. Lublin FD, Reingold SC, Cohen JA, et al. Defining the clinical course of multiple sclerosis: the 2013 revisions. Neurology 2014;83:278-86.
5. Bogosian A, Morgan M, Moss-Morris R. Multiple challenges for people after transitioning to secondary progressive multiple sclerosis: a qualitative study. BMJ Open 2019;9:e026421.
6. Multiple Sclerosis Trust. MS: the facts. https://www.mstrust.org.uk/about-ms/what-ms/ms-facts. Accessed 05-Mar-2019.
7. Office for National Statistics. Ethnicity and National Identify in England and Wales: 2011. https://www.ons.gov.uk/peoplepopulationandcommunity/culturalidentity/ethnicity/articles/ethnicityandnationalidentityinenglandandwales/2012-12-11. Accessed 26-Mar-2019. 2012.
8. Novartis Data on File. SPECTRUM Healthcare Professionals Survey.
9. Novartis Data on File. Delay in time to CDP data. 2018.
10. National Institute for Health and Clinical Excellence (NICE). Ocrelizumab for treating relapsing-remitting multiple sclerosis. Technology appraisal guidance [TA533]. https://www.nice.org.uk/Guidance/TA533. Accessed 06-Mar-2019.
11. National Institute for Health and Clinical Excellence (NICE). Beta interferons and glatiramer acetate for treating multiple sclerosis. Technology appraisal guidance [TA527]. https://www.nice.org.uk/guidance/ta527. Accessed 06-Mar-2019.
12. Palace J, Bregenzer T, Tremlett H, et al. UK multiple sclerosis risk-sharing scheme: a new natural history dataset and an improved Markov model. BMJ Open 2014;4:e004073.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Siponimod for treating secondary progressive multiple sclerosis [ID1304]

Company Technical Engagement Response Appendix A

February 2020

File name	Version	Contains confidential information	Date
Company Technical Engagement Response Appendix A	1	Yes	3rd February 2020

Contents

Tables

Figures

Abbreviations

ARR	Annualised relapse rate
CDP-3	Confirmed disability progression at 3 months
CDP-6	Confirmed disability progression at 6 months
CI	Confidence interval
HR	Hazard ratio
IFN	Interferon
IFNβ-1a	Interferon beta-1a
IFNβ-1b	Interferon beta-1b
IM	Intramuscular
ITC	Indirect treatment comparison
ITT	Intention-to-treat
IV	Intravenous
mg	Milligram
MIU	Million International Units
n/a	Not applicable
NMA	Network meta-analysis
PO	Oral
q2d	Once every 2 days (every other day)
q4w	Once every 4 weeks
qd	Once daily
qw	Once weekly
RCT	Randomised controlled trial
RR	Rate ratio
SC	Subcutaneous
SPMS	Secondary progressive multiple sclerosis
tiw	Three times weekly
TSD	Technical Support Document
µg	Microgram
µg/m^2	Microgram per square metre body surface area

Appendix A: NMAs using Active SPMS subgroup data from EXPAND

A.1 Preface

- During the technical engagement teleconference on 23rd January 2020, it was agreed by NICE and the Evidence Review Group (ERG) that Novartis would submit a Network Meta-Analysis (NMA) using Active Secondary Progressive Multiple Sclerosis (SPMS) data.
- The ERG's NMA is based on data for the full SPMS intention-to-treat (ITT) population. However, since publication of the ERG report, the licensed indication for siponimod has been confirmed as 'for the treatment of adult patients with SPMS with active disease evidenced by relapses or imaging features of inflammatory activity.'
- As discussed on the technical engagement teleconference, Novartis believes that the Matching-Adjusted Indirect Comparison (MAIC) approach submitted in the CS Document B is the most appropriate approach for indirect comparison of the efficacy of siponimod vs. interferon β-1b. However, if an unadjusted NMA is considered by the committee as an alternative scenario to MAIC, it should be in Active SPMS rather than full SPMS, so that the data used reflects the licensed indication.
- For this additional NMA, data from EXPAND were obtained from the Active SPMS sub-population instead of the ITT population. Note that the input data for the comparator trials have not been changed (i.e., these still reflect the ITT populations) because the comparator trials do not report data for the Active SPMS subgroup.
- In the EXPAND trial, the *post hoc* Active SPMS subgroup analyses included patients who experienced relapses in the two years prior to the study and/or who had gadolinium enhanced T1 lesions at baseline.
- Data were available to perform this additional analysis for Time to 3-month confirmed disability progression (CDP-3), Time to 6-month confirmed disability progression (CDP-6), and annualised relapse rate (ARR).
- Data were not available to perform this analysis for All-cause Discontinuation, or Proportion with CDP-6 at 96 weeks.

A.2 Methods

A.2.1. Evidence network geometry

Evidence network diagrams were drawn to visualise the evidence for each clinical outcome of interest (CDP-6, CDP-3, and ARR). In these figures, the available evidence was summarised such that each treatment was represented by a "node," and randomised comparisons between treatments were shown by lines linking the nodes. The thickness of each line reflects the number of studies informing the comparison. Node colours represent different treatments and the size of each node

reflects the proportionate numbers of patients randomised to each treatment. For EXPAND, only the Active SPMS subpopulation was included for this analysis.

The evidence networks were designed to include all published randomised controlled trials (RCTs) identified by the systematic searches focusing on the SPMS population, as well as EXPAND. The networks were constructed for each target outcome to reflect the interventions of interest. To maximise clinical relevance, comparator arms that differed by treatment, route of administration, dose, and/or dosing schedule were treated as distinct nodes, while similar treatments were pooled together. If it had been relevant, trials that did not share common treatment arms with any other trial would have been represented by disconnected networks.

A.2.2. Network meta-analyses

All NMAs using summary level data were performed using a Bayesian framework.[1-3] The chosen reference treatment for all analyses was placebo, given that it was the only common comparator between any studies. Only fixed-effect models were used for the NMAs due to the sparse network populated by almost exclusively single-study connections. Vague or flat priors, such as $N(0, 100^2)$, were assigned for basic parameters throughout, although informative priors were also considered.[4, 5] A binomial or normal likelihood model which accounts for the use of multi-arm trials was used for analyses, depending on the outcome. Standard indirect treatment comparison (ITC)/NMA methodology based on National Institute for Health and Care Excellence (NICE) Decision Support Unit (DSU) Technical Support Documents (TSD) was followed.[1, 6]

As a measure of the association between each treatment and its efficacy, Markov Chain Monte Carlo methods were used to model point estimates and 95% credible intervals for each pairwise comparison on outcomes of interest. Measures of effect that are commonly presented for Bayesian NMAs were generated, including mean rank with 95% credible intervals (where values closer to 1 are preferred), and probability of best (p-best), second best, and so forth.[7] Also, Surface Under the Cumulative RAnking curve (SUCRA) values were generated as an additional measure to reflect ranking and uncertainty. This measure, expressed as a percentage, showed the relative probability of an intervention being among the best options or better than other interventions.[7] For interpretation, both p(best) and SUCRA values range between 0 and 1; values nearer to 1 are preferred.[7] To assess whether fixed- or random-effects models had adequate fit to the data, the posterior mean of the residual deviance from each NMA was compared to the corresponding number of unconstrained data points (approximately equal if the fit is adequate), as well as the deviance information criterion (DIC).

All analyses were conducted using R (R Core Team, Vienna, Austria) and WinBUGS software (MRC Biostatistics Unit, Cambridge, UK) based on the WinBUGS code outlined in the NICE DSU TSD.[1, 6] Three chains were fit in WinBUGS for each analysis, with a burn-in of ≥60,000 iterations and subsequent sampling of ≥60,000 iterations.

A.3 Inputs

Table 1–Table 3 present the inputs used in the Time to CDP-3, Time to CDP-6, and ARR networks.

Table 1: Inputs for time to confirmed disability progression at 3 months

Study ID	Treatment	Sample Size	HR	Lower CI	Upper CI	p value	Ln(HR)	SE of HR	Source
EXPAND (ITT Population)	PO Placebo qd	546	n/a	n/a	n/a	n/a	n/a	n/a	Figure 2A, Kappos 2018
	PO Siponimod 2 mg qd	1099	0.79	0.65	0.95	0.0134	−0.235722334	0.096808577	
EXPAND (Active SPMS Subgroup)	PO Placebo qd	[redacted]	n/a	n/a	n/a	n/a	n/a	n/a	Data on file (see NICE Single Technology Appraisal, Document B, Table 26)
	PO Siponimod 2 mg qd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
SPECTRIMS	SC Placebo tiw	205	n/a	n/a	n/a	n/a	n/a	n/a	Table 2 (Planned analysis), SPECTRIMS Study Group 2001 (Clinical outcomes)
	SC 22 µg IFN-beta-1a tiw	209	0.88	0.69 [a]	1.12 [a]	0.305	−0.127833372	0.123427704	
	SC 44 µg IFN-beta-1a tiw	204	0.83	0.65	1.07	0.146	−0.186329578	0.12715346	
European	SC Placebo q2d	358	n/a	n/a	n/a	n/a	n/a	n/a	Figure 2, Kappos 2001
	SC 8 MIU IFN-beta-1b q2d	360	0.74 [b]	0.60 [a,b]	0.91 [a,b]	0.007	−0.301183474	0.104570947	
IMPACT	IM Placebo qw	219	n/a	n/a	n/a	n/a	n/a	n/a	Results (paragraph 5), Cohen 2002
	IM 60 µg IFN-beta-1a qw	217	0.98	0.68	1.41	0.90	−0.023268627	0.185865798	

[a] Error was calculated from the rate ratio and p value.[8]
[b] The HR and/or CI were not reported in the publication. Missing values were estimated by digitising and curve-fitting the reported Kaplan–Meier curve for time to CDP.[9]
Abbreviations: CDP: confirmed disability progression; CI: confidence interval; HR: hazard ratio; IFNβ: interferon-beta; IM: intramuscular; MIU: million international units; mg: milligram; n/a: not applicable; PO: oral; qd: once daily; q2d: once every other day; qw: once weekly; SC: subcutaneous; SE: standard error; tiw: three times weekly; µg: microgram.

Table 2: Inputs for time to confirmed disability progression at 6 months

Study ID	Treatment	Sample Size	HR	Lower CI	Upper CI	p value	Ln(HR)	Ln(SE)	Source
EXPAND (ITT Population)	PO Placebo qd	546	n/a	n/a	n/a	n/a	n/a	n/a	Figure 2B, Kappos 2018
	PO Siponimod 2 mg qd	1099	0.74	0.6	0.92	0.0058	−0.301105093	0.109041841	
EXPAND (Active SPMS Subgroup)	PO Placebo qd	[redacted]	n/a	n/a	n/a	n/a	n/a	n/a	Data on file (see NICE Single Technology Appraisal, Document B, Table 27)
	PO Siponimod 2 mg qd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
North American	SC Placebo q2d	308	n/a	n/a	n/a	n/a	n/a	n/a	Figure 2, Panitch 2004
	SC 250 µg IFN-beta-1b q2d	317	0.92 [a]	0.71 [a]	1.20 [a]	0.6060	−0.077996137	0.133351604	
	SC 22 µg IFN-beta-1a qw	186	1.13	0.82	1.57	0.45	0.122217633	0.165695551	

[a] The HR and/or CI were not reported in the publication. Missing values were estimated by digitising and curve-fitting the reported Kaplan–Meier curve for time to CDP.[9]

Abbreviations: CDP: confirmed disability progression; CI: confidence interval; HR: hazard ratio; IFNβ: interferon beta; mg: milligram; n/a: not applicable; PO: oral; qd: once daily; q2d: once every other day; qw: once weekly; SC: subcutaneous; SE: standard error; µg: microgram.

Table 3: Inputs for annualised relapse rate

Study ID	Treatment	Sample Size	ARR	Rate Ratio for ARR vs. Placebo	Lower CI	Upper CI	p value	Ln(RR)	SE of RR	Source
EXPAND (ITT Population)	PO Placebo qd	546	0.16	n/a	n/a	n/a	n/a	n/a	n/a	Table 2, Kappos 2018
	PO Siponimod 2 mg qd	1099	0.07	0.45	0.34	0.59	<0.0001	−0.798507696	0.140606357	
EXPAND (Active SPMS Subgroup)	PO Placebo qd	[redacted]	[redacted]	n/a	n/a	n/a	n/a	n/a	n/a	Data on file (see NICE Single Technology Appraisal, Document B, Table 28, "Adjusted ARR")
	PO Siponimod 2 mg qd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
ASCEND	IV Placebo q4w	448	0.17	n/a	n/a	n/a	n/a	n/a	n/a	Table e4 (Appendix), Kapoor 2018
	IV Natalizumab q4w	439	0.08	0.453	0.323	0.634	<0.001	−0.791863153	0.172039957	
SPECTRIMS	SC Placebo tiw	205	0.71	n/a	n/a	n/a	n/a	n/a	n/a	Table 3, SPECTRIMS Study Group 2001 (Clinical Results)
	SC 22 µg IFN-beta-1a tiw	209	0.50	0.69	0.56	0.84	<0.001	−0.371063681	0.103434977	
	SC 44 µg IFN-beta-1a tiw	204	0.50	0.69	0.56	0.85	<0.001	−0.371063681	0.106453971	
North American	SC Placebo q2d	308	0.28	n/a	n/a	n/a	n/a	n/a	n/a	Table (E)T-1 (Supplementary), Panitch 2004
	SC 250 µg IFN-beta-1b q2d *Equivalent: SC 8 MIU IFN-beta-1b q2d*	317	0.16	0.571 [a]	0.375 [b]	0.870 [b]	0.009	−0.559615788	0.214685507	
European	SC Placebo q2d	358	0.57	n/a	n/a	n/a	n/a	n/a	n/a	Table 1, Kappos 2001
	SC 8 MIU IFN-beta-1b q2d	360	0.42	0.737 [a]	0.473 [c]	1.078 [c]	0.003	−0.30538165	0.210144735	

	Equivalent: SC 250 µg IFN-beta-1b q2d									
	SC 22 µg IFN-beta-1a qw	186	0.27	0.9	0.64	1.27	0.55	−0.105360516	0.17482245	
IMPACT	IM Placebo qw	219	0.30	n/a	n/a	n/a	n/a	n/a	n/a	Results (Relapse Rate section), Cohen 2002
	IM 60 µg IFN-beta-1a qw	217	0.20	0.667 [a]	0.494 [b]	0.900 [b]	0.008	−0.405465108	0.153025318	

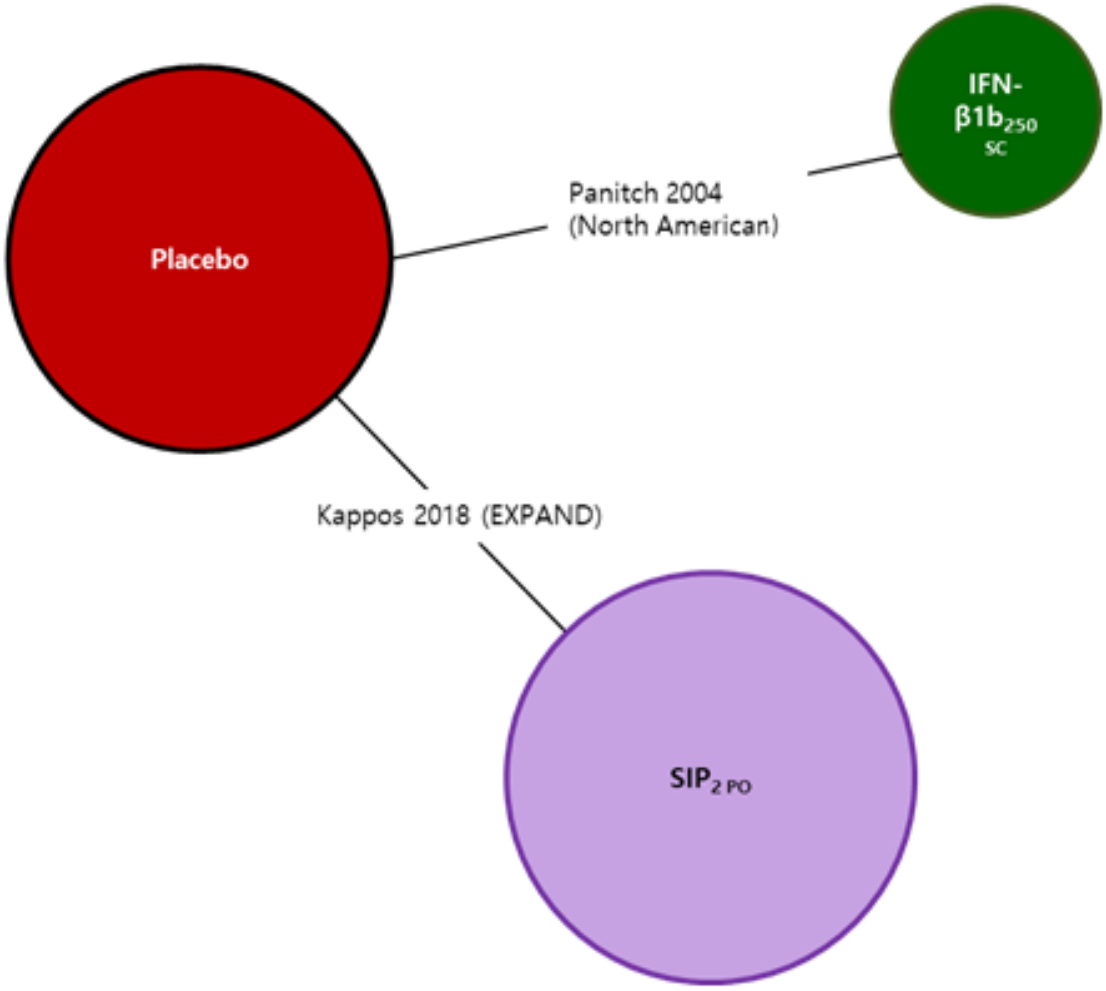
[a] Rate ratio was not reported in the publication; it was calculated by dividing the ARR of the treatment arm by the placebo arm.
[b] Error was calculated from the reported p value, and the reported or calculated rate ratio.[8]
[c] Error has been estimated using the CI from the North American SG 160 µg/m^2 treatment arm (95% CI = 0.473 – 1.078) which has a similar effect size (RR = 0.714) and sample size (n = 314). The Handling Continuous Outcomes in Quantitative Synthesis guide recommends that studies only missing error should not be excluded as this can lead to a biased combined estimate.[10]
Abbreviations: ARR: annualised relapse rate; CI: confidence interval; IFNβ: interferon beta; IM: intramuscular; MIU: million international units; mg: milligram; n/a: not applicable; PO: oral; qd: once daily; q2d: once every other day; qw: once weekly; q4w: once every four weeks; RR: rate ratio; SC: subcutaneous; SE: standard error; tiw: three times weekly; µg: microgram.

A.4 Results

A.4.1. Evidence networks

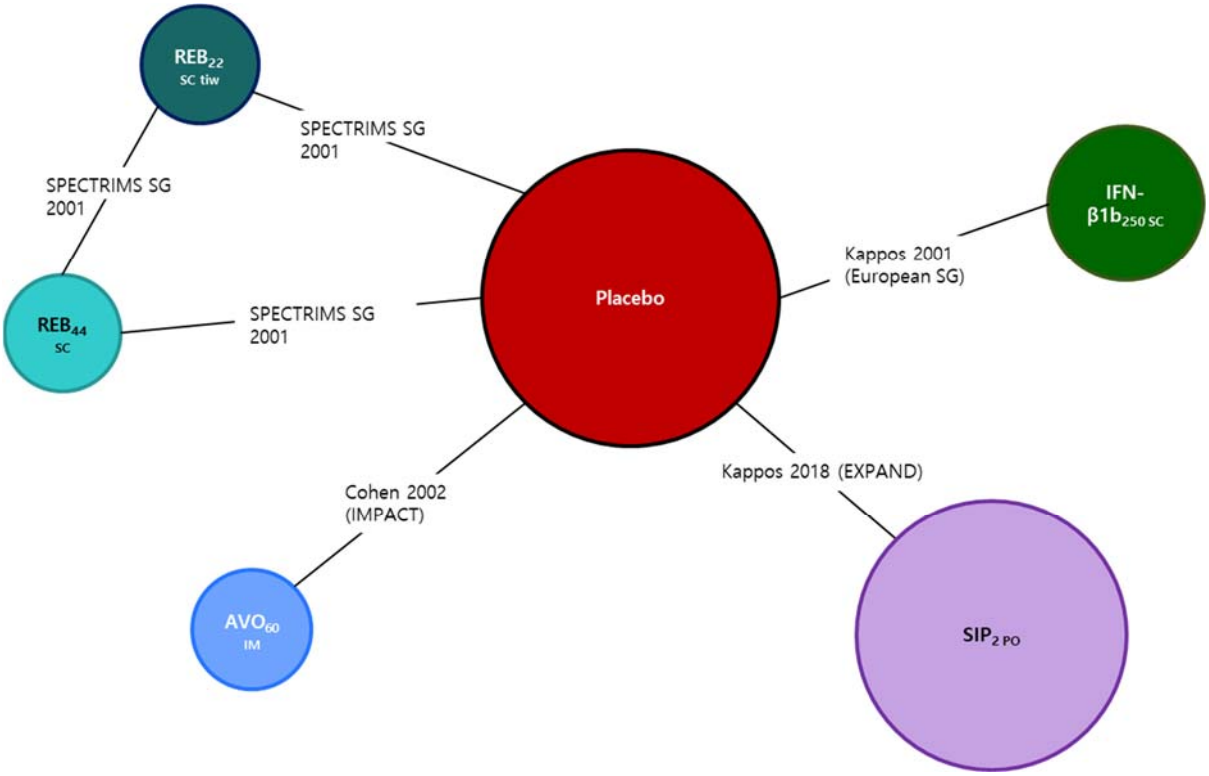
The evidence networks for the outcomes of CDP-6, CDP-3, and ARR are presented in Figure 1–Figure 3.

Figure 1: Network diagram for time to confirmed disability progression at 6 months



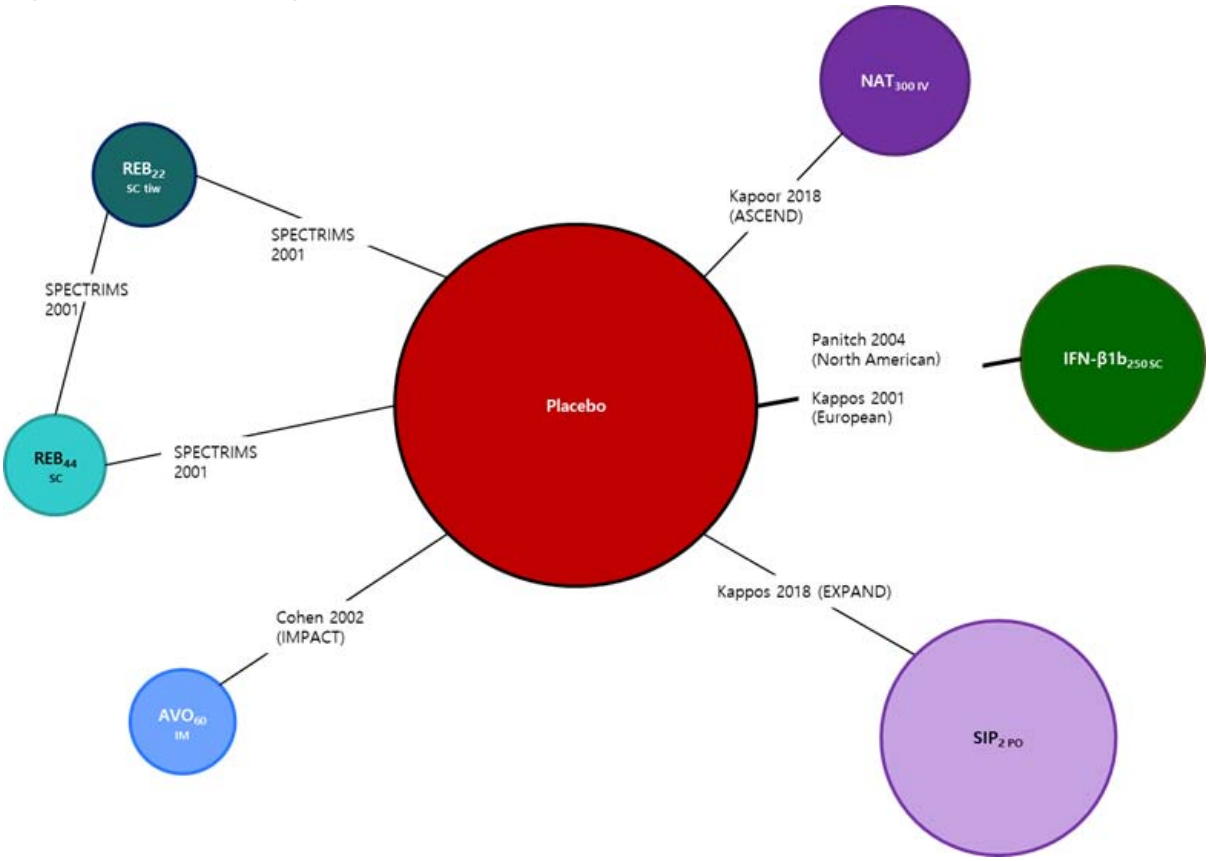
Abbreviations: IFNβ-1b$_{250}$: interferon-beta-1b 250 micrograms; PO: oral; SC: subcutaneous; SIP$_2$: siponimod 2 milligrams.

Figure 2: Network diagram for time to confirmed disability progression at 3 months



Abbreviations: AVO_{60}: Avonex® (IFNβ-1a) 60 micrograms; IFNβ-$1b_{250}$: interferon-beta-1b 250 micrograms; IM: intramuscular; PO: oral; REB_{22}: Rebif® (IFNβ-1a) 22 micrograms; REB_{44}: Rebif® (IFNβ-1a) 44 micrograms; SC: subcutaneous; SIP_2: siponimod 2 milligrams; tiw: three times weekly.

Figure 3: Network diagram for annualised relapse rate



Abbreviations: AVO_{60}: Avonex® (IFNβ-1a) 60 micrograms; $IFNβ\text{-}1b_{250}$: interferon-beta-1b 250 micrograms; IM: intramuscular; IV: intravenous; NAT_{300}: natalizumab 300 milligrams; PO: oral; qw: once weekly; REB_{22}: Rebif® (IFNβ-1a) 22 micrograms; REB_{44}: Rebif® (IFNβ-1a) 44 micrograms; SC: subcutaneous; SIP_2: siponimod 2 milligrams.

A.4.2. League tables

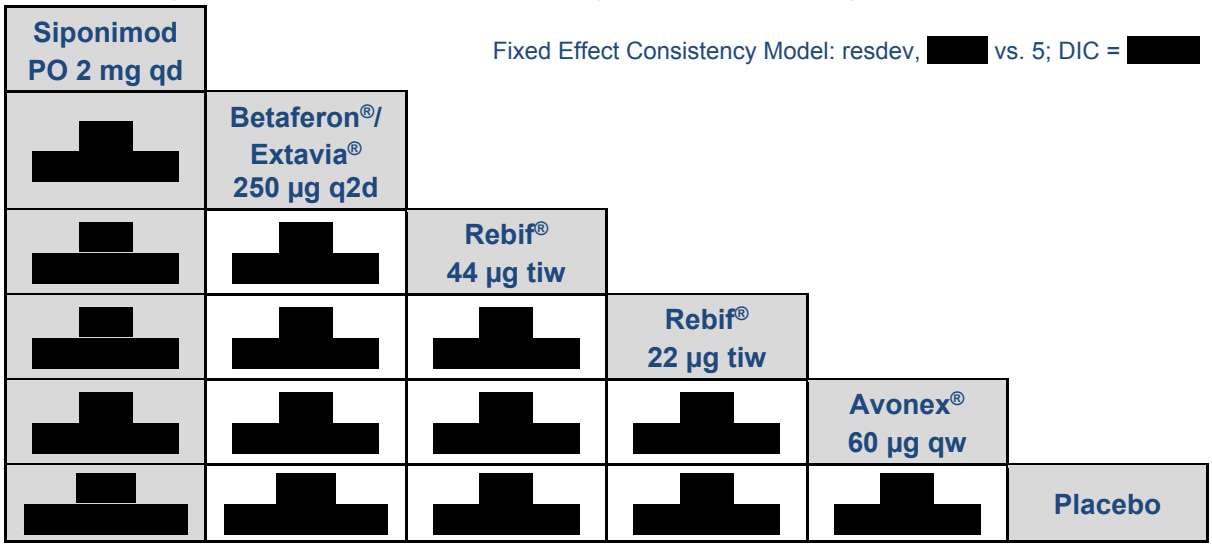
The results of the NMAs are presented as league tables in Table 4–Table 6. All results are presented as rate ratio (RR), or hazard ratio (HR) (95% credible interval), as appropriate. An RR or HR < 1 indicates that the intervention to the upper left had a more favourable outcome than the intervention to the lower right. Statistically significant results are bolded.

Table 4: League table for time to CDP-6 using Active SPMS subgroup data for EXPAND

Siponimod PO 2 mg qd	Fixed Effect Consistency Model: resdev, [redacted] vs 2; DIC = [redacted]	
[redacted]	**Betaferon®/Extavia® 250 µg q2d**	
[redacted]	[redacted]	**Placebo**

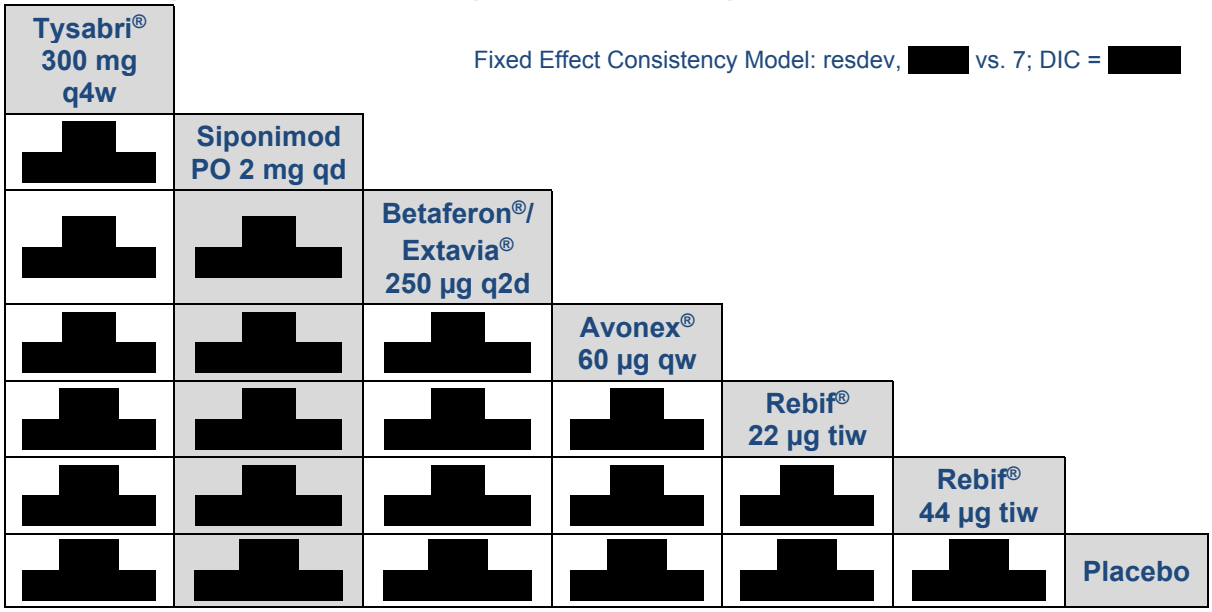
Results are HR (95% credible interval). HR < 1 suggests upper left intervention is better. Statistically significant values are bolded.
Betaferon®/Extavia® = SC interferon-beta-1b.
Abbreviations: CDP-6: confirmed disability progression at 6 months; DIC: deviance information criterion; HR: hazard ratio; PO: oral; qd: once daily; q2d: every other day; resdev: residual deviance; SC: subcutaneous.

Table 5: League table for time to CDP-3 using Active SPMS subgroup data for EXPAND



Results are HR (95% credible interval). HR < 1 suggests upper left intervention is better. Statistically significant values are bolded.
Avonex® = IM IFN-beta-1a; Betaferon®/Extavia® = SC IFN-beta-1b; Rebif® = SC IFN-beta-1a.
Abbreviations: CDP-3: Confirmed disability progression at 3 months; DIC: deviance information criterion; HR: hazard ratio IFNβ-1a: interferon beta-1a; IFNβ-1b: interferon beta-1b; IM: intramuscular; NMA: network meta-analysis; PO: oral; qd: once daily; qw: once weekly; q2d: every other day; resdev: residual deviance; SC: subcutaneous; tiw: three times weekly.

Table 6: League table for ARR using Active SPMS subgroup data for EXPAND



Results are RR (95% credible interval). RR < 1 suggests upper left intervention is better. Statistically significant values are bolded.
Avonex® = IM IFN-beta-1a; Betaferon®/Extavia® = SC IFN-beta-1b; Rebif® = SC IFN-beta-1a; Tysabri® = IV natalizumab.
Abbreviations: ARR: annualised relapse rate; DIC: deviance information criterion; IFN: interferon; qd: once daily; qw: once weekly; q4w: every four weeks; resdev: residual deviance; RR: rate ratio; SC: subcutaneous; tiw: three times weekly.

Table 7: Summary of P-best and SUCRA results

Intervention (administration)	Study ID(s)	Sample Size	Mean P-best (%)	Mean SUCRA (%)
Time to CDP-6				
Placebo	All studies in network	[redacted]	[redacted]	[redacted]
Siponimod (PO 2 mg qd)	EXPAND[11] (Active SPMS subgroup)	[redacted]	[redacted]	[redacted]
Betaferon®/Extavia® IFNβ-1b (SC 250 µg q2d)	North American Study[12]	317	[redacted]	[redacted]
Time to CDP-3				
Placebo	All studies in network	[redacted]	[redacted]	[redacted]
Siponimod (PO 2 mg qd)	EXPAND[11] (Active SPMS subgroup)	[redacted]	[redacted]	[redacted]
Rebif® IFNβ-1a (SC 22 µg tiw)	SPECTRIMS[13, 14]	209	[redacted]	[redacted]
Rebif® IFNβ-1a (SC 44 µg tiw)	SPECTRIMS[13, 14]	204	[redacted]	[redacted]
Betaferon®/Extavia® IFNβ-1b (SC 250 µg q2d)	European Study[15, 16]	360	[redacted]	[redacted]
Avonex® IFNβ-1a (IM 60 µg qw)	IMPACT[17]	217	[redacted]	[redacted]
ARR				
Placebo	All studies in network	[redacted]	[redacted]	[redacted]
Siponimod (PO 2 mg qd)	EXPAND[11] (Active SPMS subgroup)	[redacted]	[redacted]	[redacted]
Tysabri® Natalizumab (IV 300 mg q4w)	ASCEND[18]	439	[redacted]	[redacted]
Rebif® IFNβ-1a (SC 22 µg tiw)	SPECTRIMS[13, 14]	209	[redacted]	[redacted]
Rebif® IFNβ-1a (SC 44 µg tiw)	SPECTRIMS[13, 14]	204	[redacted]	[redacted]
Betaferon®/Extavia® IFNβ-1b (SC 250 µg q2d)	North American Study[12] European Study[15, 16]	677	[redacted]	[redacted]
Avonex® IFNβ-1a (IM 60 µg qw)	IMPACT[17]	217	[redacted]	[redacted]

Abbreviations: ARR: annualised relapse rate; CDP-3: 3-month confirmed disability progression; CDP-6: 6-month confirmed disability progression; IFN: interferon; IM: intramuscular; PO: oral; SC: subcutaneous; tiw: three times weekly; qd: once daily; q2d: every other day; qw: once weekly; q4w: every four weeks.

A.4.3. Summary of results

For the base case comparison, siponimod vs interferon β-1b, the Active SPMS NMA results in HRs that are more favourable for CDP-3 and CDP-6, but a RR that is less favourable for ARR, compared with the ERG's ITT NMA (certainty around the relative effect for ARR may be affected

by the absolute number of events in the subgroup vs the ITT). Table 8 compares the results for siponimod vs comparators across the Active SPMS NMA, the ERG's ITT NMA, and the MAIC. The economic model utilises treatment vs placebo data. As such, due to there being only a single link in the network (input data for ARR were pooled across the North American and European studies), the model inputs for siponimod and interferon β-1b when utilising the Active SPMS NMA are unchanged compared to the technical team's model version (which uses the Active SPMS subgroup data in the non-MAIC settings).

Table 8: MAIC base case results and Active SPMS NMA results for all outcomes compared to the ERG's ITT NMA

Siponimod vs comparator	MAIC	Active SPMS NMA	ERG ITT NMA
Time to CDP-6, HR (95% CI / 95% CrI)			
Betaferon®/Extavia® (SC IFNβ-1b 250 µg q2d)	[redacted]	[redacted]	0.80 (0.57–1.13)
Time to CDP-3, HR (95% CI / 95% CrI)			
Betaferon®/Extavia® (SC IFNβ-1b 250 µg q2d)	[redacted]	[redacted]	1.07 (0.81–1.41)
Rebif® (SC IFNβ-1a 44 µg tiw)	[redacted]	[redacted]	**0.79 (0.66–0.95)**
Rebif® (SC IFNβ-1a 22 µg tiw)	[redacted]	[redacted]	0.90 (0.66–1.22)
Avonex® (IM IFNβ-1a 60 µg qw)	[redacted]	[redacted]	0.81 (0.54–1.22)
ARR ratio, RR (95% CI / 95% CrI)			
Betaferon®/Extavia® (SC IFNβ-1b 250 µg q2d)	[redacted]	[redacted]	0.65 (0.46–1.04)
Avonex® (IM IFNβ-1a 60 µg qw)	[redacted]	[redacted]	0.67 (0.45–1.00)
Rebif® (SC IFNβ-1a 22 µg tiw)	[redacted]	[redacted]	**0.65 (0.47–0.91)**
Rebif® (SC IFNβ-1a 44 µg tiw)	[redacted]	[redacted]	**0.65 (0.46–0.92)**

Statistically significant values are bolded.
Abbreviations: ARR: annualised relapse rate; CDP-3: 3-month confirmed disability progression; CDP-6: 6-month confirmed disability progression; CI: confidence interval; CrI: credible interval; ERG: Evidence Review Group; HR: hazard ratio; IM: intramuscular; IFN: interferon; NMA: network meta-analysis; qw: once weekly; q2d: every other day; RR: rate ratio; SC: subcutaneous; SPMS: secondary progressive multiple sclerosis; tiw: three times weekly.

Compared to the ERG's ITT NMA, the Active SPMS NMA uses input data that are more reflective of the licensed indication. However, given the reasons outlined in CS Document B surrounding the substantial heterogeneity between the different trials, the MAIC still remains the most appropriate method of indirect comparison for siponimod in SPMS.

References

1. Dias S, Sutton AJ, Ades A, et al. Evidence synthesis for decision making 2: a generalized linear modeling framework for pairwise and network meta-analysis of randomized controlled trials. Medical Decision Making 2013;33:607-617.
2. Dias S, Sutton AJ, Welton NJ, et al. Evidence synthesis for decision making 3: heterogeneity—subgroups, meta-regression, bias, and bias-adjustment. Medical Decision Making 2013;33:618-640.
3. Dias S, Welton NJ, Sutton AJ, et al. Evidence synthesis for decision making 4: inconsistency in networks of evidence based on randomized controlled trials. Medical Decision Making 2013;33:641-656.
4. Turner RM, Davey J, Clarke MJ, et al. Predicting the extent of heterogeneity in meta-analysis, using empirical data from the Cochrane Database of Systematic Reviews. International journal of epidemiology 2012;41:818-827.
5. Rhodes KM, Turner RM, Higgins JP. Predictive distributions were developed for the extent of heterogeneity in meta-analyses of continuous outcome data. Journal of Clinical Epidemiology 2015;68:52-60.
6. Dias S, Welton NJ, Sutton AJ, et al. Evidence synthesis for decision making 1: introduction. Medical decision making 2013;33:597-606.
7. Salanti G, Ades A, Ioannidis JP. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. Journal of clinical epidemiology 2011;64:163-171.
8. Altman DG, Bland JM. How to obtain the confidence interval from a P value. Bmj 2011;343:d2090.
9. Bormann I. DigitizeIt. 2016.
10. Fu R, Vandermeer BW, Shamliyan TA, et al. Handling Continuous Outcomes in Quantitative Synthesis. Methods Guide for Effectiveness and Comparative Effectiveness Reviews. Rockville (MD): Agency for Healthcare Research and Quality (US), 2013.
11. Kappos L, Bar-Or A, Cree BAC, et al. Siponimod versus placebo in secondary progressive multiple sclerosis (EXPAND): a double-blind, randomised, phase 3 study. Lancet 2018;391:1263-1273.
12. Panitch H, Miller A, Paty D, et al. Interferon beta-1b in secondary progressive MS: results from a 3-year controlled study. Neurology 2004;63:1788-95.
13. Li DK, Zhao GJ, Paty DW. Randomized controlled trial of interferon-beta-1a in secondary progressive MS: MRI results. Neurology 2001;56:1505-13.
14. SPECTRIMS Study Group. Randomized controlled trial of interferon- beta-1a in secondary progressive MS: Clinical results. Neurology 2001;56:1496-504.
15. European Study Group. 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 1998;352:1491-7.
16. Kappos L, Polman C, Pozzilli C, et al. Final analysis of the European multicenter trial on IFNbeta-1b in secondary-progressive MS. Neurology 2001;57:1969-75.
17. Cohen JA, Cutter GR, Fischer JS, et al. Benefit of interferon beta-1a on MSFC progression in secondary progressive MS. Neurology 2002;59:679-87.
18. Kapoor R, Ho PR, Campbell N, et al. Effect of natalizumab on disease progression in secondary progressive multiple sclerosis (ASCEND): a phase 3, randomised, double-blind, placebo-controlled trial with an open-label extension. Lancet Neurol 2018;17:405-415.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Siponimod for treating secondary progressive multiple sclerosis [ID1304]

Company Technical Engagement Response Appendix B

February 2020

File name	Version	Contains confidential information	Date
Company Technical Engagement Response Appendix B	1	Yes	10th Feburary 2020

Contents

Tables

Figures

Abbreviations

CDP	Confirmed disability progression
CI	Confidence interval
ERG	Evidence Review Group
HR	Hazard ratio
ICER	Incremental cost-effectiveness ratio
ITT	Intention-to-treat
MAIC	Matching-adjusted indirect comparison
MS	Multiple sclerosis
NMA	Network meta-analysis
PAS	Patient Access Scheme
QALY	Quality-adjusted life year
RPSFT	Rank-preserving structural failure time
SDMT	Symbol Digit Modalities Test

Appendix B: Additional supporting data for the technical engagement

This appendix has been provided with permission from NICE (via email on 4th Feburary 2020) as an additional response to the issue of modelling long-term treatment effect raised by the technical team and discussed on the Technical Engagement call on 23rd January. It should be read alongside our response to the Technical Report dated 10th February.

As per our response to the Technical Report (see section 4, pages 9–10), Novartis does not agree with any application of treatment effect waning for siponimod as there is no clinical evidence to support this assumption. This appendix provides new evidence to further support this position.

B.1 Extrapolating the effects of treatment beyond the follow up period in the clinical trials

B.1.1. EXPAND trial Extension phase data

6-month confirmed-disability progression (CDP) up to 6-years

Our submission provided data on 6-month CDP up to 5.5 years. These new data reflect the latest available follow-up period of 6 years.

As highlighted in our submission, following the Core part of the EXPAND trial, all patients continuing into the Extension phase ([redacted] patients, [redacted] of the original 1651 randomised patients) were switched on to open-label siponimod, and information on long-term efficacy and safety are being recorded for up to 7 years (the Extension part of the trial is still ongoing at the time of this appraisal).

A rank-preserving structural failure time (RPSFT) model was used on the time to CDP Kaplan–Meier curves to correct the placebo arm for crossing over to siponimod treatment, by modelling how the placebo arm would have looked if the placebo patients had not crossed over to open-label siponimod. We acknowledge that RPSFT analyses are not as robust as placebo-controlled data but it is important to note that conducting long-term placebo-controlled trials in multiple sclerosis (MS) would be unethical given the evidence from EXPAND that siponimod is proven in the core part of the study to be an efficacious treatment. As such, RPSFT analyses are the best available source of evidence to inform long-term treatment effect.

Figure 1 presents the Kaplan–Meier curves for time to 6-month CDP for siponimod, the combined Core and Extension results for the placebo arm, and the RPSFT-corrected placebo-arm data. Table 1 presents the hazard ratio (HR) results for the analysis at 72 months (6 years).

The HR for 6-month CDP for siponimod compared with RPSFT-corrected placebo after 6 years is [redacted] (95% CI: [redacted]). This is compared with a HR of 0.74 (95% CI: 0.60–0.92) at the end of the Core part of the EXPAND trial and a HR of [redacted] (95% CI: [redacted]) at the 5.5 year time-point, which was presented in Section B.2.6.8 of CS Document B.

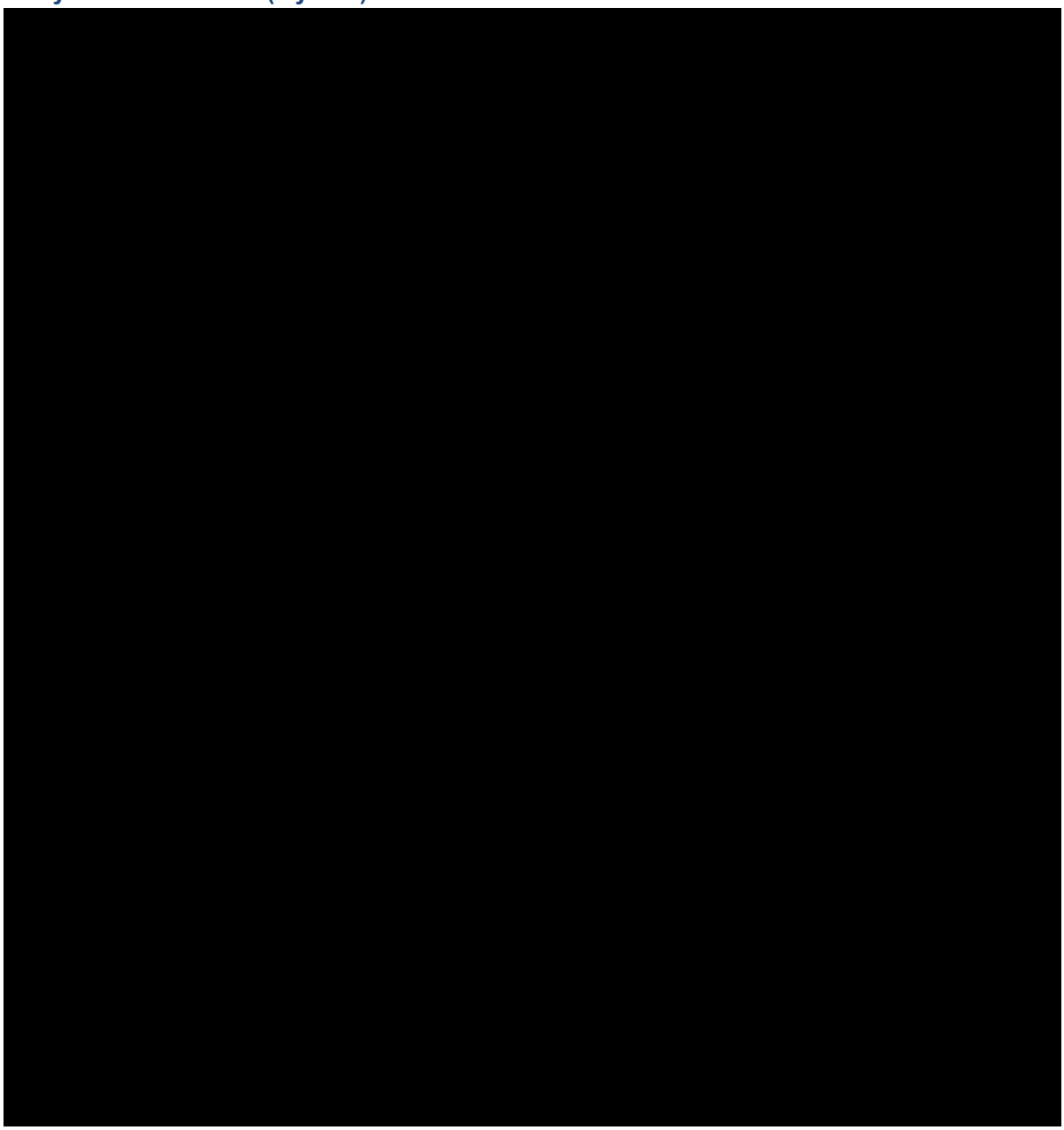
The 6-year data do not change the interpretation of the results of the long-term follow-up data compared with the previously submitted 5.5-year data but provide the most up-to-date results, showing that treatment effect has been maintained for siponimod over the duration of the Extension phase of the trial.

Table 1: Time to 6-month CDP – placebo corrected for cross-over to open-label siponimod using RPSFT model – analysis at 72 months (6 years)

Number of placebo patients receiving open-label siponimod, N (%)	[redacted]
Number of placebo patients receiving open-label siponimod before 6-month CDP, N (%)	[redacted]
Combined Core and Extension – ITT, HR (95% CI)	[redacted]
RPSFT acceleration factor, psi (95% CI)	[redacted]
After RPSFT correction, HR (95% CI)	[redacted]

Abbreviations: CDP: confirmed disability progression; CI: confidence interval; HR: hazard ratio; ITT: intention-to-treat; RPSFT: rank-preserving structural failure time.

Figure 1: Time to 6-month CDP data from the Extension phase of the EXPAND trial – analysis at 72 months (6 years)



Placebo corrected for cross-over to open-label siponimod using an RPSFT model.
Abbreviations: CDP: confirmed disability progression; RPSFT: rank-preserving structural failure time.

Symbol Digit Modalities Test (SDMT) up to 5-years[1]

Our submission provided data on cognitive processing speed up to 2 years. These new data reflect the latest available follow up period of 5 years. This is important because benefits of cognition are not captured in the cost-effectiveness analysis. If arbitrary waning assumptions are applied to EDSS-based efficacy in the model, this would result in underestimation of siponimod cost-effectiveness given that sustained benefits on cognition are observed.

Of the [redacted] patients entering the Extension phase of the trial, [redacted] ([redacted]) were ongoing at the 36-month Extension data cut-off (total study duration ≤ 5 years).

Time to 6-month confirmed worsening on SDMT was [redacted] in the continued siponimod group (received siponimod in Core and Extension) versus the placebo switching group (received placebo in Core and switched to siponimod in Extension, not cross-over corrected) (p=[redacted]).

Additionally, risk of worsening on the SDMT, measured as a decrease of ≥4 points (with a change of ≥4 points being deemed clinically meaningful) was [redacted] by [redacted] (HR [redacted]; 95% CI: [redacted]), corresponding to a delay of [redacted] for the 25th percentile (continued siponimod group vs placebo switching group, not cross-over corrected: [redacted] vs [redacted] months). This is compared to a 21% risk reduction measured at the end of the Core study for siponimod compared with placebo (HR 0.79; 95% CI: 0.65, 0.96), as presented in Section B.2.6.6, page 52 of CS Document B.

These results indicate a sustained treatment effect for siponimod on cognitive benefits for up to 5 years.

B.1.2. Additional scenarios incorporating treatment waning

Novartis disagrees with application of treatment effect waning for siponimod in cost-effectiveness analysis. However, having reflected on the technical enagagement discussions, waning scenario analyses are provided to allow the Committee to explore uncertainty.

Novartis does not support the validity of the NICE technical team's suggestion to see analyses of efficacy decreasing for siponimod by 50% after 5 years or 25% after 2 years and 50% after 5 years.

As stated in Table 51, Section B.3.2.2, page 96 of CS Document B, the Novartis base case considers all-cause treatment discontinuation to act as a proxy for treatment waning, consistent with the recent ocrelizumab appraisal (TA533) in which the Committee agreed with this approach in the absence of any clinical evidence for waning. But following the request from the NICE technical team, the following scenarios have been provided to allow the Committee to explore uncertainty in the long-term treatment effect of siponimod:

- A scenario aligned with the assumptions used in the NICE appraisal of beta interferons and glatiramer acetate (TA527, the appraisal of the most appropriate comparator for siponimod, Extavia®). In this scenario, a sudden 50% reduction in efficacy is applied from Year 11.[2]
- A conservative scenario in which waning begins the cycle after the latest long-term data follow-up for siponimod. In this scenario, efficacy is modelled to wane in a tapered fashion with a 25% reduction from Year 7 then a 50% reduction from Year 10; this scenario applies the tapered waning assumptions suggested in the Technical Report, but with later onset supported by the RPSFT data showing no evidence of waning up to 6 years.

Given the lack of clinical evidence for loss of treatment effect, any modelled waning should be equally applied to both siponimod and interferon β-1b (Extavia). Table 2 presents the cost-effectiveness results of applying these assumptions, however, given the reasons outlined in the Technical Engagement Response and in the CS Document B, any application of treatment waning is unreasonable, arbitrary and not founded in evidence.

Table 2: Cost-effectiveness results for treatment waning scenarios

Model Settings	Incremental costs	Incremental QALYs	ICER
Technical Report: Technical Team's preferred assumptions as presented in the Technical Report: ERG base case + 1–3, efficacy from "company MAIC" *NB*: this model used time-constant discontinuation instead of the Technical Team's expressed preference for the exponential curve for time-dependent discontinuation	[redacted]	1.67	[redacted]
Revised base case: Technical Report model above + Corrected to use exponential curve for time-dependent discontinuation, as intended by Technical Team **Discontinuation as a proxy for waning** (Novartis revised base case for Technical Engagement)	[redacted]	1.30	[redacted]
Scenario 1: Novartis revised base case for Technical Engagement **+50% waning from year 11** (aligns with NICE MTA assumption)	[redacted]	1.21	[redacted]
Scenario 2: Novartis revised base case for Technical Engagement **+25% waning from year 7 then 50% waning from year 10** (tapered waning after 6-year extension data)	[redacted]	1.14	[redacted]

Abbreviations: ERG: Evidence Review Group; ICER: incremental cost-effectiveness ratio; MAIC: matching-adjusted indirect comparison; NMA: network meta-analysis; PAS: Patient Access Scheme; QALY: quality-adjusted life year.

In summary, application of waning scenarios that account for long-term follow-up data for siponimod and precedent in a relevant MS appraisal for the main comparator, result in ICERs for siponimod vs interferon β-1b of approximately [redacted] per QALY gained (compared to a base case ICER of [redacted] per QALY).

References

1. Novartis Data on File. Long-term Efficacy and Safety of Siponimod in Patients with SPMS: EXPAND Extension Analysis up to 5 Years. Abstract to be presented at AAN 2020.
2. National Institute for Health and Clinical Excellence (NICE). Beta interferons and glatiramer acetate for treating multiple sclerosis. Technology appraisal guidance [TA527]. https://www.nice.org.uk/guidance/ta527. Accessed 06-Mar-2019.

NICE National Institute for Health and Care Excellence

Technical engagement response form

Siponimod for treating secondary progressive multiple sclerosis [ID1304]

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholders responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments **Monday 10 February 2020**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- 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.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. 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.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- 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 replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	**Caroline Smith**
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Questions for engagement

Issue 1: Positioning of siponimod in the treatment pathway	
a) What relapse and MRI criteria are used to diagnose active secondary progressive MS? Does this align with the definition of active secondary progressive MS used in the siponimod clinical trial of "relapses in 2 years prior to study or gadolinium-enhanced T1 lesions at baseline"?	
b) What proportion of patients are diagnosed with active secondary progressive MS without a prior diagnosis of relapsing-remitting MS?	
c) Would siponimod be used in the same position in the treatment pathway as interferon beta-1b (Extavia)?	**No, but there would be overlap. Extavia could start for RRMS and continue through the transition, then be stopped. Whereas siponimod would start in the transition then continue for longer**
d) Would the availability of an additional treatment for active secondary progressive MS change the point at which active secondary progressive MS is diagnosed in clinical practice?	**Doubtful**
e) Would siponimod displace therapies for relapsing-remitting MS used during the transition period in clinical practice?	**possibly**

Issue 2: Generalisability of the trial results to the NHS	
a) Are the characteristics of participants in the EXPAND trial likely to reflect the characteristics of people with active secondary progressive MS seen in practice in the NHS?	
Issue 3: Indirect treatment comparisons	
a) Are the results for the EXPAND full trial population generalisable to the active subgroup?	
b) Is the company's matching-adjusted indirect comparison or the ERG's exploratory network meta-analysis the most appropriate source of efficacy data for the model?	
Issue 4: Extrapolating the effects of treatment beyond the follow up period in the clinical trials	
a) Would the efficacy of siponimod be expected to diminish over time?	It seems likely but no evidence provided
b) Would patients (who do not meet the stopping criteria described in the NHS England treatment algorithm) continue to be treated with siponimod if treatment efficacy reduces over time?	From the submission yes, but I think this should be kept under review by clinicians and stopping should be an option
Issue 5: Source of natural history data	

a) Is it appropriate for the model to include the possibility that during the natural course of secondary progressive MS patients may improve EDSS state?	No
Issue 6: Treatment discontinuation	
a) Which of the estimates of the number of patients remaining on treatment is more plausible?	
Issue 7: Utility values	
a) Which health state utility values are more plausible? EXPAND supplemented by Orme et al. or Orme et al. alone?	Orme et al alone

NICE National Institute for Health and Care Excellence

Technical engagement response form

Siponimod for treating secondary progressive multiple sclerosis [ID1304]

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholders responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments **Monday 10 February 2020**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- 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.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. 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.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- 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 replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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)	**Multiple Sclerosis Trust**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Questions for engagement

Issue 1: Positioning of siponimod in the treatment pathway	
a) What relapse and MRI criteria are used to diagnose active secondary progressive MS? Does this align with the definition of active secondary progressive MS used in the siponimod clinical trial of "relapses in 2 years prior to study or gadolinium-enhanced T1 lesions at baseline"?	**We believe that the definitions used for active secondary progressive MS in EXPAND would be appropriate. It would be reasonable to assume that a relapse in previous two years or MRI evidence would indicate MS activity.** **The concept of active/not active was introduced by Lublin et al 2014 Neurology. According to the Lublin definition of active secondary progressive MS, activity is determined by clinical relapses assessed at least annually and/or MRI activity (contrast-enhancing lesions; new and unequivocally enlarging T2 lesions), progression measured by clinical evaluation, assessed at least annually. There is no indication of frequency of imaging.**
b) What proportion of patients are diagnosed with active secondary progressive MS without a prior diagnosis of relapsing-remitting MS?	**To the best of our knowledge, this number is not known.** **In our submission, we reported that 22% (n=55) of respondents to our survey stated that they had been diagnosed secondary progressive MS (SPMS) without prior diagnosis of relapsing remitting MS (RRMS).** **We are not aware of published studies which give figures for the number of people diagnosed with SPMS without prior diagnosis of RRMS and certainly none which report numbers with active SPMS without prior diagnosis of RRMS.** **Our main reason for highlighting this finding from our survey was to ensure that this group of people with SPMS was not inadvertently excluded from treatment with siponimod by the wording used in NICE guidance, which might assume prior RRMS diagnosis.**

c) Would siponimod be used in the same position in the treatment pathway as interferon beta-1b (Extavia)?	**Yes, in theory Extavia can be prescribed for secondary progressive MS with continuing relapses. In practice, the prescribing levels for Extavia are very low, largely due to difficulties with preparing injections from solvent and powder.**
d) Would the availability of an additional treatment for active secondary progressive MS change the point at which active secondary progressive MS is diagnosed in clinical practice?	**Yes, potentially. In the absence of treatments for secondary progressive MS, in clinical practice active secondary progressive MS is probably classified as relapsing remitting MS to allow continued access to disease modifying drugs.**
e) Would siponimod displace therapies for relapsing-remitting MS used during the transition period in clinical practice?	**Yes, potentially. With the availability of a treatment for active secondary progressive MS, neurologists may be willing to discuss with patients evidence of transition at an earlier stage and may recommend switching from the patient's current treatment for relapsing remitting MS.**
Issue 2: Generalisability of the trial results to the NHS	
a) Are the characteristics of participants in the EXPAND trial likely to reflect the characteristics of people with active secondary progressive MS seen in practice in the NHS?	**Yes, on the whole we believe so. Slightly over a quarter of the participants in the EXPAND study had EDSS of 3-4.5; in current practice, clinicians might be reluctant to diagnose secondary progressive MS until the patient has more significant walking difficulties, possibly when someone reaches EDSS 5 or greater.**
Issue 3: Indirect treatment comparisons	
a) Are the results for the EXPAND full trial population generalisable to the active subgroup?	**No, we do not believe they are. While the baseline data may be broadly similar, we would argue that presence of relapses or MRI activity in the active subgroup indicates a significant difference in the factors driving increased disability. We also note that the European marketing authorisation for siponimod is for active secondary progressive MS, ie**

	people experiencing relapses or showing signs of inflammation in MRI scans. We believe it is more appropriate to use data from this subgroup. **This would be consistent with TA585 which also assessed efficacy using data from the active subgroup (in this case active primary progressive MS).**
b) Is the company's matching-adjusted indirect comparison or the ERG's exploratory network meta-analysis the most appropriate source of efficacy data for the model?	**No comment.**
Issue 4: Extrapolating the effects of treatment beyond the follow up period in the clinical trials	
a) Would the efficacy of siponimod be expected to diminish over time?	**Over time, it is likely that the apparent effectiveness of siponimod would be reduced, simply because the active, inflammatory component of MS (against which siponimod is effective) would be a less significant contributor to overall disability worsening and neurodegeneration a more significant contributor.** **This does not necessarily indicate an intrinsic loss of efficacy of siponimod.**
b) Would patients (who do not meet the stopping criteria described in the NHS England treatment algorithm) continue to be treated with siponimod if treatment efficacy reduces over time?	**We would anticipate that treatment with siponimod will be subject to an annual review similar to that followed for relapsing remitting treatments. If there was evidence that siponimod was no longer effective, for example increasing EDSS in the absence of relapses or MRI activity, then it would be discontinued.**
Issue 5: Source of natural history data	
a) Is it appropriate for the model to include the possibility that during the natural	**It is possible for EDSS to improve. Just as for relapsing remitting MS, if someone with active secondary progressive MS has had a relapse, their EDSS may increase due to the effects of the relapse, then decrease again (ie improve) as they recover from the relapse.**

course of secondary progressive MS patients may improve EDSS state?	**It is inappropriate to assume that this will only occur over short timeframes and that regressions are likely to be very rare.**
Issue 6: Treatment discontinuation	
a) Which of the estimates of the number of patients remaining on treatment is more plausible?	**No comment.**
Issue 7: Utility values	
a) Which health state utility values are more plausible? EXPAND supplemented by Orme et al. or Orme et al. alone?	**EQ-5D values from the EXPAND study reflect the actual measures for the study population so we would support using EXPAND supplemented by Orme et al.**

NICE National Institute for Health and Care Excellence

Technical engagement response form

Siponimod for treating secondary progressive multiple sclerosis [ID1304]

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholders responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments **Monday 10 February 2020**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- 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.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. 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.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- 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 replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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)	**Association of British Neurologists**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Questions for engagement

Issue 1: Positioning of siponimod in the treatment pathway	
a) What relapse and MRI criteria are used to diagnose active secondary progressive MS? Does this align with the definition of active secondary progressive MS used in the siponimod clinical trial of "relapses in 2 years prior to study or gadolinium-enhanced T1 lesions at baseline"?	**A relapse in the past 2 years and/or evidence of new activity on CNS MRI. This almost aligns with the trial definition however new T2 lesions are allowed in this definition, whereas the trial required gadolinium enhancement, which is fleeting [one lesion enhances for 4-6 weeks] so does not capture all new lesions.**
b) What proportion of patients are diagnosed with active secondary progressive MS without a prior diagnosis of relapsing-remitting MS?	**All patients with secondary progressive MS have – by definition – previously had relapsing-remitting MS. Only a low proportion [<10% of secondary progressive patients] are not diagnosed during the relapsing-remitting phase,**
c) Would siponimod be used in the same position in the treatment pathway as interferon beta-1b (Extavia)?	**Interferon-beta may be used in people with secondary progressive MS who have had at least two disabling relapses in the previous two years. This is similar, but not the same as the definition of "active" secondary progressive MS proposed for the marketing authorisation for siponimod.** **Although this use is permitted, the committee should be aware that interferon-beta is used only rarely in this subgroup; most UK MS neurologists are not convinced it offers a useful effect.**
d) Would the availability of an additional treatment for active secondary progressive MS change the point at which active	**Yes, much more attention would be given to diagnosing this subgroup.**

secondary progressive MS is diagnosed in clinical practice?	
e) Would siponimod displace therapies for relapsing-remitting MS used during the transition period in clinical practice?	**Yes**
Issue 2: Generalisability of the trial results to the NHS	
a) Are the characteristics of participants in the EXPAND trial likely to reflect the characteristics of people with active secondary progressive MS seen in practice in the NHS?	**Yes. The subgroup Designated "active" in the EXPAND trial are typical of active secondary progressive MS seen in NHS practice.**
Issue 3: Indirect treatment comparisons	
a) Are the results for the EXPAND full trial population generalisable to the active subgroup?	**It is likely that the active subgroup will show a greater treatment effect that the full trial population. This is the experience of the trials of natalizumab in secondary progressive MS and ocrelizumab in primary progressive MS.**
b) Is the company's matching-adjusted indirect comparison or the ERG's exploratory network meta-analysis the most appropriate source of efficacy data for the model?	**Siponimod is the first drug to have shown definite benefit in this group of patients. Therefore, comparative data is hard to find.** **For the reasons in 3a) it is not appropriate to use the full trial population for the indirect comparison.**
Issue 4: Extrapolating the effects of treatment beyond the follow up period in the clinical trials	

a) Would the efficacy of siponimod be expected to diminish over time?	**If the main action is to suppress inflammation (which is not certain), then it would be expected to diminish with time. However, the time limited trial data does not demonstrate this.**
b) Would patients (who do not meet the stopping criteria described in the NHS England treatment algorithm) continue to be treated with siponimod if treatment efficacy reduces over time?	**Yes. But those who have evidence of unaffected rate of disease progression could stop or those that lose the ability to walk.**
Issue 5: Source of natural history data	
a) Is it appropriate for the model to include the possibility that during the natural course of secondary progressive MS patients may improve EDSS state?	**Yes - these patients are highly susceptible to fluctuations and it is often hard to exclude the possibility of subtle relapses. Likewise the natural history studies of Weinshenker in the 1990s of the London Ontario database, suggests that people with secondary progressive MS experience disability improvement in roughly one out of every ten years.**
Issue 6: Treatment discontinuation	
a) Which of the estimates of the number of patients remaining on treatment is more plausible?	**We cannot advise between the exponential or Weibull estimates.**
Issue 7: Utility values	
a) Which health state utility values are more plausible? EXPAND supplemented by Orme et al. or Orme et al. alone?	**Previous technology appraisals have used Orme alone, so it seems fair to apply the same utility analysis.**

NICE National Institute for Health and Care Excellence

Technical engagement response form

Siponimod for treating secondary progressive multiple sclerosis [ID1304]

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholders responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments **Monday 10 February 2020**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- 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.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. 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.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- 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 replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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)	**Roche Product Ltd**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Questions for engagement

Issue 1: Positioning of siponimod in the treatment pathway	
a) What relapse and MRI criteria are used to diagnose active secondary progressive MS? Does this align with the definition of active secondary progressive MS used in the siponimod clinical trial of "relapses in 2 years prior to study or gadolinium-enhanced T1 lesions at baseline"?	The diagnosis of secondary progressive multiple sclerosis is made retrospectively in clinical practice, following a period of steady worsening in disability over **at least 12 month**, **sometimes 2 years**, in the absence of relapse activity. This is also reflected in the NHSE DMT treatment algorithm for stopping criteria of disease modifying treatments for relapsing remitting multiple sclerosis, as well as the starting criteria for Extavia. The submission positions Siponimod for active secondary progressive multiple sclerosis, where diagnosis has been based on a steady worsening of disability over **6 months** (with relapse and/or MRI activity). There has been no evidence presented to support this change in criteria used to identify secondary progressive patients for treatment with siponimod. These criteria are not reflective of the licensed indication of siponimod, nor the current definitions of SPMS in the ABN guidelines, NHSE treatment algorithm, or clinical practice. Nor are they reflective of the available evidence, as patients in the EXPAND study required EDSS progression in the 2 years prior in order to be included in the trial. Shortening the period of time for a patient to demonstrate disability progression to be diagnosed with SPMS creates additional uncertainty with regard to the diagnosis in a population requiring superimposed relapses and/or MRI activity. Disability changes over a shorter period of time may be resulting from relapse-related symptoms rather that true progression.
b) What proportion of patients are diagnosed with active secondary progressive MS without a prior diagnosis of relapsing-remitting MS?	

c) Would siponimod be used in the same position in the treatment pathway as interferon beta-1b (Extavia)?	
d) Would the availability of an additional treatment for active secondary progressive MS change the point at which active secondary progressive MS is diagnosed in clinical practice?	
e) Would siponimod displace therapies for relapsing-remitting MS used during the transition period in clinical practice?	
a) Are the characteristics of participants in the EXPAND trial likely to reflect the characteristics of people with active secondary progressive MS seen in practice in the NHS?	
Issue 3: Indirect treatment comparisons	
a) Are the results for the EXPAND full trial population generalisable to the active subgroup?	
b) Is the company's matching-adjusted indirect comparison or the ERG's exploratory network meta-analysis the most appropriate source of efficacy data for the model?	

Issue 4: Extrapolating the effects of treatment beyond the follow up period in the clinical trials	
a) Would the efficacy of siponimod be expected to diminish over time?	
b) Would patients (who do not meet the stopping criteria described in the NHS England treatment algorithm) continue to be treated with siponimod if treatment efficacy reduces over time?	
Issue 5: Source of natural history data	
a) Is it appropriate for the model to include the possibility that during the natural course of secondary progressive MS patients may improve EDSS state?	
Issue 6: Treatment discontinuation	
a) Which of the estimates of the number of patients remaining on treatment is more plausible?	There may be a class effect of rebound inflammatory activity to consider with siponimod when it is discontinued, even in patients with seemingly no relapse activity. Rebound effect is well characterised with fingolimod, an in-class S1P analogue.
Issue 7: Utility values	
a) Which health state utility values are more plausible? EXPAND supplemented by Orme et al. or Orme et al. alone?	

Title: *Multiple sclerosis (secondary progressive) - Siponimod [ID1304]: ERG critique of the company response to Technical Engagement*

Produced by	Warwick Evidence
Authors	Peter Auguste, Research Fellow, Warwick Evidence Alexander Tsertsvadze, Senior Researcher, Warwick Evidence Mubarak Patel, Research Assistant, Warwick Evidence Chris Stinton, Senior Research Fellow, Warwick Evidence Felix Achana, Senior Research Fellow, Warwick Evidence Jacoby Patterson, Senior Researcher, Warwick Evidence Rachel Court, Information Specialist, Warwick Evidence Anna Brown, Information Specialist, Warwick Evidence Olga Ciccarelli, Professor of Neurology, University College of London Carl Counsell, Clinical reader, University of Aberdeen Xavier Armoiry, Honorary Clinical Research Fellow, Warwick Evidence Aileen Clarke, Professor of Public Health, Warwick Evidence Amy Grove, Assistant Professor, Warwick Evidence
Correspondence to	Dr Amy Grove A.L.Grove@warwick.ac.uk
Date completed	17/02/2020

Source of funding: This report was commissioned by the NIHR HTA Programme as project number 12/97/79.

Declared competing interests of the authors

Prof. Carl Counsell received funding through Biogen-Idec, who provided some funding for a departmental MS nurse.

Prof. Olga Ciccarelli received consultancy fees from Novartis, Biogen-Idec and General-Electric, Genzyme, All payments were made to her employer, UCL Institute of Neurology. She also received reimbursement for attending a symposium from Novartis and ECTRIMS, and funds for research from the UK MS Society, EPSRC, UCLH and BRC.

Rider on responsibility for report

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

Table of Contents

1 SUMMARY

The objective of this report is to provide a critique of the company's response to the Technical Engagement (TE) for Siponimod for treating secondary progressive multiple sclerosis (SPMS) [ID1304]. The company submitted the following:

1. An exploratory active SPMS network meta-analysis (NMA) (appendix A)
2. An updated economic model which allows efficacy waning to be implemented in the model equally for siponimod and the comparator
3. An appendix with the company response to technical engagement:
    a. A new base case incremental cost-effectiveness ratios (ICER) with time-dependent discontinuation using an exponential curve
    b. A scenario analysis ICER to demonstrate the impact of waning 50% from year 11
    c. A scenario analysis ICER to demonstrate the impact of waning 25% from year 7 and 50% from year 10
    d. EXPAND long term disability progression data up to 6 years
    e. EXPAND long-term cognition data up to 5 years.

The ERG critique responds to Issues 1 to 7 of the company TE engagement response in Sections 1.1 to 1.7. We have examined the company's responses or assumptions and provided a critique, as well as aimed to reproduce the ICERs (see Section 1.8), which were based on a revised model submitted by the company.

1.1 Issue 1: Positioning of siponimod in the treatment pathway

The ERG have no further comment on questions 1a-e. Please refer to the ERG response contained in the ERG TE response form.

1.2 Issue 2: Generalisability of the trial results to the NHS

The ERG have no further comment regarding this issue. Please refer to the ERG response contained in the ERG TE response form.

1.3 Issue 3. Indirect treatment comparisons

1.3.1.1 Issue 3 a. "Are the results for the EXPAND full trial population generalisable to the active subgroup?"

The ERG highlight that the *post hoc* active SPMS subgroup population from the EXPAND trial was presented in the CS due to uncertainty as to the final licensed population for siponimod. This license is now in place (see Section 1.3.1.3).

A total of [redacted] (47.2% of the full analysis set) out of 1651 patients made up the active SPMS subgroup ([redacted] in siponimod, [redacted] in placebo). This was consistent with the 2:1 randomisation of the overall trial. As stated in the ERG TE response, we compared the two groups via visual inspection of the patient baseline characteristics and consider them to be broadly similar (ITT see Table 6 [pg 34-35], active see Table 25 of the CS Document B [page 59] and in section E.2.1 in the CS appendices [page 145]). The ERG found the following differences:

- Siponimod ITT population were significantly [redacted] than their active SPMS counterparts
- the ITT population group had significantly [redacted] duration since MS diagnosis
- and the ITT population group had significantly [redacted] duration since first symptoms compared to the active sub-group.

The company TE response states that "*the numbers of relapses and Gd+ lesions at baseline are markedly different between the ITT and Active SPMS subgroup"*. The ERG checked and confirm that these two characteristics were different between the ITT and the active groups (active SPMS had greater number of relapses).

A comparison of primary and secondary endpoints for the ITT population and active SPMS subgroup is presented in Table 1. The company state that *"the efficacy results in the Active SPMS subgroup are meaningfully better than those in the full SPMS population"*. The ERG note that, at the 5% level, the hazard ratios and adjusted rate ratio ratios are not statistically significantly different between the ITT and active SPMS populations (see Table 1).

Table 1. Primary and secondary endpoints for the ITT population and active SPMS subgroup

	Active SPMS subgroup		ITT population	
	Siponimod	**Placebo**	**Siponimod**	**Placebo**
	[redacted]	[redacted]	1099	546
Time to 3-month CDP (primary endpoint)				
Number of progressions (%)	[redacted]	[redacted]	288 (26.3)	173 (31.7)
HR for progression (95% CI)	[redacted]		0.79 (0.65, 0.95)	
p-value	[redacted]		0.0134	
Time to 6-month CDP (secondary endpoint)				
Number of progressions (%)	[redacted]	[redacted]	218 (19.9)	139 (25.5)
HR for progression (95% CI)	[redacted]		0.74 (0.60, 0.92)	
p-value	[redacted]		0.0058	
Annualised Relapse Rate (ARR) for confirmed relapses				
Adjusted ARR (95% CI)	[redacted]	[redacted]	0.071 (0.055, 0.092)	0.160 (0.123, 0.207)
ARR ratio (95% CI)	[redacted]		0.445 (0.337, 0.587)	
p-value	[redacted]		< 0.0001	
Time to first confirmed relapse				
Number with events (%)	[redacted]	[redacted]	113 (10.7)	100 (18.9)
HR (95% CI)	[redacted]		0.54 (0.41, 0.70)	
p-value	[redacted]		< 0.0001	

ITT: Intention to treat; HR: Hazard ratio; CI: Confidence intervals; CDP: Confirmed disability progression; ARR: Annualised Relapse Rate; SPMS: Secondary progressive multiple sclerosis

The ERG emphasise that the efficacy estimates from the subgroup populations were not planned in the design of the EXPAND trial. Given the evidence available, the ERG consider the active SPMS population to be comparable to the ITT population. However, without access to the IPD we are unable to make a formal assessment.

We note the company TE response to 3a, and the original company statement that "*a MAIC focussing on active SPMS specifically is not possible*" (clarification response A21d).

1.3.1.2 Issue 3 b. "Is the company's matching-adjusted indirect comparison or the ERG's exploratory network meta-analysis the most appropriate source of efficacy data for the model?"

In the TE response, the company asserts their view that the MAIC analysis presented in CS Document B is the most appropriate approach to indirectly compare siponimod with other disease-modifying treatments (DMTs). The ERG refer to Section 4.4 and 4.5 of the ERG report for a critique of the company MAIC.

We note that the company refer to the "*NICE Decision Support Unit (DSU) Technical Support Document (TSD) 18"* in the TE response. The ERG note that section 4.2.8 of NICE TSD 18 (page 65-66), provides a list of reporting items that should be addressed explicitly in the presentation of a MAIC. The ERG consider that many of these items were not listed in the CS (see appendix 1).

The ERG checked the following statement *"the data used in the model by the Technical Team in their "efficacy from NMA" analyses presented in table 1 of the Technical Report are in fact a naïve comparison of the Active subgroup of EXPAND with the North American study"* and can confirm that this is correct after rounding (where applicable).

1.3.1.3 Indirect comparison and/or multiple treatment comparison

There have been no randomised clinical trials (RCTs) comparing head-to-head siponimod with other (DMTs) licensed for MS or used in clinical practice for treatment of SPMS across the UK. Six RCTs conducted in patients with SPMS were identified in the CS SLR. The EXPAND[2] trial and five additional studies were double-blind placebo-controlled randomised trials of natalizumab (ASCEND study),[4] interferon beta-1b (EU study, NA study),[7-9] and interferon beta-1a (SPECTRIMS study, IMPACT study).[5, 6, 10]

The company TE response (Appendix A) includes a series of NMAs based on active SPMS subgroup data from EXPAND study. The company state that *"if an unadjusted NMA were to be considered by the Appraisal Committee as an alternative scenario, the NMA should utilise the data from the post hoc Active SPMS subgroup rather than the full SPMS ITT population that was used in the Evidence Review Group's (ERG) exploratory NMA. This is because these data reflect the license for siponimod and most closely reflect the population that would be treated in NHS clinical practice."* The ERG support the statement that the active SPMS subgroup reflects the license for siponimod "*…for the treatment of adult patients with SPMS with active disease evidenced by relapses or imaging features of inflammatory activity*" (Company TE response, Page 5; Appendix A).

1.3.1.4 ERG critique of the company NMA

The ERG consider that the company's justification would have been well grounded if the active SPMS subgroup NMA had been based on active SPMS subgroup data across all trials included in the NMA. However, the company NMA relies on the active SPMS subgroup data solely from the EXPAND study owing to the company's access to individual patient data of this trial. None of the other trials included in NMA had provided active SPMS subgroup data, thereby rendering the NMA feasibility for active SPMS patients problematic. The company clearly states "*the input data for the*

comparator trials have not been changed (i.e., these still reflect the ITT populations)". The active subgroup NMA cannot be assumed as one for active SPMS patients, therefore it is lacking relevance due to being based on ITT population samples (except for EXPAND trial) of trials that enrolled both relapsing and non-relapsing SPMS.

Nevertheless, the company conducted a placebo-anchored NMA that includes the synthesis of active SPMS subgroup data of EXPAND trial (siponimod)[2] and ITT-based (full sample) data from five RCTs of comparator treatments in patients with SPMS.[4 5, 6, 10 7-9] (Table 2).

Table 2. Studies included the company-conducted network meta-analysis

Study Name Year	**Interventions (dose, frequency) sample size (n)**
EXPAND study 2018	Active SPMS subgroup Siponimod (2 mg PO QD); n=516 Placebo; n=263
ASCEND study 2018	Natalizumab (300 mg IV Q4W); n=439 Placebo; n=448
SPECTRIMS study 2001	Interferon beta-1a (22 µg SC TIW); n=209 Interferon beta-1a (44 µg SC TIW); n=204 Placebo; n=205
NA study 2004	Interferon beta-1b (160 µg SC Q2D); n=314 – not used in the NMA synthesis Interferon beta-1b (250 µg SC Q2D); n=317 Placebo; n=308
EU study 1998, 2001	Interferon beta-1b (250 µg SC Q2D); n=360 Placebo; n=358
IMPACT study 2002	Interferon beta-1a (60 µg IM QW); n=217 Placebo; n=219
NA=North American; EU=European; IV=intravenous; PO=oral; QD=once daily; SC=subcutaneous; TIW=three times a week; Q2D=once every two days; Q4W=once every 4 weeks; IM=intramuscular; QW=once weekly; NR=not reported	

The outcomes analysed for the NMA were a) confirmed disability progression at 3 months (CDP-3), b) CDP-6, and c) annualised relapse rate (ARR). All-cause discontinuation and proportion with CDP-6 at 96 weeks were not reported.

The statistical and modeling methods as well as the results output (network plots, league tables, and Surface Under Cumulative RAnking Curve[SUCRAs]) were presented adequately (company TE Response: Appendix A; pages 5-15). However, rankograms were missing. Analyses were undertaken in WinBUGS, using a Bayesian framework and fixed models only due to the sparsity of the networks. Vague priors were assigned for basic parameters. Informative priors were "*considered*", but the ERG found no statement regarding whether or not they were actually used as a sensitivity analysis, what the priors were defined as, and if they altered results.

Markov Chain Monte Carlo methods were used to model estimates and 95% credible intervals for each pairwise comparison for each outcome. Mean rank, probability of best and SUCRA curve values

were generated to ascertain the ranking of treatments and uncertainty. Chains in WinBUGS were fit with a burn-in of ≥60,000 iterations and subsequent sampling of ≥60,000, although exact numbers were not reported.

Tables 1-3 of the company TE report Appendix A, present the inputs used in the NMA for each outcome. This includes treatment, sample size, hazard ratio (HR), 95% confidence interval, p-value of HR, log (HR), the standard error of the HR, and the source of the information. The ERG note that some values were estimated, where applicable, due to them not being reported in the publication for that study, for example the HR in the European Study.

The results of the NMAs are presented in Tables 4-6 in the company TE report (Appendix A), where results <1 indicated the treatment in the upper left had a more favourable outcome.

- Table 4 reports the NMA results for time to 6-month CDP using a fixed effects model, which compares siponomod, interferon-beta-1b (betaferon) and placebo. Siponimod was shown to be statistically significantly better than placebo, but not compared to interferon-beta-1b, HR = [redacted]
- Table 5 reports the NMA results for time to 3-month CDP using a fixed effects model. Results indicated that siponimod was statistically significantly better than placebo ([redacted]), but not compared to the other four treatments
- Table 6 reports the NMA results for ARR using a fixed effects model. Siponimod was statistically significantly better than placebo ([redacted]), but not significantly better than the other five treatments included in the comparison. Moreover, siponimod was shown to be worse than natalizumab (Tysabri 300mg q4w), although this result was not statistically significant.

In the comparisons for all of the outcomes, siponimod was only significantly better than placebo.

The company TE report (Appendix A) Table 7 summarised the probability of each treatment being the best-ranked treatment (mean p-best), and the SUCRA results. Values close to 100% are preferred. For the CDP-3 and CDP-6 outcomes, siponimod had the highest mean p-best (CDP-6: [redacted] and CDP-3: [redacted]), and similarly for mean SUCRA (CDP-6: [redacted] and CDP-3: [redacted]). For ARR, natalizumab had the highest mean P-best and SUCRA ([redacted] and [redacted], respectively). The distribution of studies contributing to each outcome (TE response: Appendix A: network plot Figures 1-3) in the NMA were as follows:

<u>CDP-3</u>

- EXPAND study (active SPMS subgroup): siponimod vs. placebo
- SPECTRIMS study (ITT sample): interferon beta-1a (two different doses) vs. placebo

- EU study (ITT sample): interferon beta-1b vs. placebo
- IMPACT study (ITT sample): interferon beta-1a vs. placebo

CDP-6

- EXPAND study (active SPMS subgroup): siponimod vs. placebo
- North American trial (ITT sample): interferon beta-1b vs. placebo

ARR

- EXPAND study (active SPMS subgroup): siponimod vs. placebo
- ASCEND (ITT sample): natalizumab vs. placebo
- SPECTRIMS study (ITT sample): interferon beta-1a (two different doses) vs. placebo
- EU study (ITT sample): interferon beta-1b vs. placebo
- IMPACT study (ITT sample): interferon beta-1a vs. placebo
- North American trial (ITT sample): interferon beta-1b vs. placebo.

The ERG notes that for ARR, the EU study and NA study were pooled (interferon beta-1b vs. placebo).

1.3.1.5 Weaknesses and areas of uncertainty

The ERG described the cross-trial differences (study design [study duration, placebo administration mode], populations [study inclusion/exclusion criteria, baseline patient characteristics], placebo-arm outcomes [annualised relapse and discontinuation rates], and outcome definitions [for time to CDP] in the ERG report, and noted the weaknesses of both the NMA and MAIC approaches for determining efficacy data for the model (see ERG report Section 4.5.5).

Consequently, the heterogeneity across the trials synthesised in the active SPMS subgroup NMA presented in Appendix A (company TE response) weakens the credibility of the findings of indirect comparisons between siponimod and other eligible comparators (e.g., interferon beta-1b, natalizumab, interferon beta-1a) which can lead to biased treatment effect estimates.

Standard NMA relies on aggregate-level data and therefore, is unable to adjust for the differences in inclusion/exclusion criteria and baseline characteristics, some or all of which may turn out to be strong effect modifier(s). The MAIC approach, utilises individual-level data to attempt to overcome these problems. However, the ERG consider that the results of MAIC analysis presented in the CS should be viewed with caution due to unaccounted for cross-trial heterogeneity in population characteristics, a small effective sample size (ESS), limited relevance of the comparator treatment trial

populations and limited applicability of results to the target populations of patients with active SPMS (further details are provided in ERG report Section 4.4).

Summary

The key limitation of the company NMA is that it is a synthesis of the active SPMS subgroup data from EXPAND study, with the reported total sample-based (i.e., intention-to-treat) aggregate data from other five trials. The ERG consider that the total samples of SPMS patients from these five trials do not represent active SPMS patients. Those studies which did report active SPMS subgroups used slightly different definitions (see Table 3), but none of the studies reported the baseline characteristics of the active SPMS subgroup. Therefore, assumptions cannot be made about the comparability between the baseline characteristics.

Data presented in Table 3 demonstrates that the proportion of relapsing SPMS patients prior to the study in all trials (except for EU trial) was under 50%. The EU trial population included 70% of active SPMS patients. However, even with this relatively high proportion of relapsing patients, it should not be assumed that the EU trial only included active SPMS patients. The results of the EXPAND study had indicated that the effect of siponimod was modified (i.e., greater clinical benefit) in active SPMS subgroups and relapsing patients. Such non-uniform distribution across the NMA network undermines the credibility of the NMA submitted by the company.

Table 3. Active SPMS patients in EXPAND vs. other randomised controlled studies included in the company's network meta-analysis

Study name year	Inclusion of active SPMS patients	Definition of active SPMS	Availability of active SPMS subgroup aggregate data	Patients with relapses prior to study n/N (%)
EXPAND study 2018	Included	Presence of relapses in 2 years before study or Gd+ T1 lesions at baseline	Available (n=779)	596/1,651 (36.0)
SPECTRIMS study 2001	Included	Presence of relapses in the 2 years preceding the study	Not available	292/618 (47.2)
EU study 1998, 2001	Included	Relapse within 2 years before the study	Not available	502/718 (70.0)
NA study 2004	Unknown	Not defined	Not available	422/939 (45.0)
ASCEND study 2018	Unknown	Not defined	Not available	260/887 (29.3)
IMPACT study 2002	Included	Presence of relapses in year before enrolment	Not available	172/436 (39.4)

N=total sample size; NA=North American; EU=European

The use of the placebo arm as the anchor (i.e., common comparator) is another limitation. A common comparator allows the use of the relative effects of each trial to derive a relative effect for the indirect treatment comparison, thereby preserving the randomisation within the trials. However, if the assumed common comparator differs in some way (e.g., dose, route of administration, frequency) across the trials included NMA, the transitivity assumption is likely to be violated. Thus, the ERG consider that the company's use of placebo as the common comparator in the NMA to compare siponimod with other DMTs problematic, simply because in the EXPAND trial placebo was given orally (once daily), whereas in other trials placebo was given either subcutaneously, intravenously, or intramuscularly with differing frequencies. The ERG note that this limitation applies to the ERG exploratory NMA provided in the ERG report (Section 4.5). The differences in annualised relapse and discontinuation rates in the placebo arms across the trials are provided in Table 4 for completeness.

Table 4. Placebo arms: annualised relapse and discontinuation rates in EXPAND vs. other randomised controlled studies included in the company's network meta-analysis

Feature	EXPAND study 2018	SPECTRIMS study 2001	EU study 1998, 2001	NA study 2004	ASCEND study 2018	IMPACT study 2002
Sample size	n=546	n=205	n=358	n=308	n=448	n=219
Route of administration	Oral	Subcutaneous	Subcutaneous	Subcutaneous	Intravenous	Intramuscular
Dose/frequency	Once daily	3 times weekly	Once every 2 days	Once every 2 days	Once every 4 weeks	Once weekly
Annualised relapse rates	0.16	0.71	0.57	0.28	0.17	0.30
Annualised discontinuation rates	0.084	0.057	0.132	0.093	0.186	0.142
NA=North American; EU=European						

The company pooled the EU study and NA study for the comparison of ARR between interferon beta-1b 250 µg versus placebo within the network (company TE response: Appendix A; Figure 3, page 13). The ERG note the problems of pooling the above studies due to the clinical heterogeneity in study populations and discrepant efficacy results with respect to CDP between the two trials. Specifically, when EU study showed a clinical benefit of interferon beta-1b in reducing significantly CDP compared to placebo (HR=0.74, 95% CI: 0.60, 0.91), the NA study did not (HR=0.92, 95% CI: 0.71, 1.20) (company TE response: Appendix A; Tables 1-2). The EU study included more young patients with active or relapsing disease compared to NA study. These differences may fully or partially explain the benefit of interferon beta-1b in delaying disability observed in the EU study. Further indication of heterogeneity across EU and NA studies is the difference in the placebo-based ARR (0.57 vs. 0.28, respectively) (Table 4).

Section A.4.3 of the company TE response summarises the results of the NMA and compares them to the original company MAIC and the ERG NMA, which are collated in TE response Table 8. The

company argue that since the results of the active-SPMS NMA are more reflective of the licensed indication, it is preferred to the ERG NMA, but the MAIC is still the most appropriate. The ERG note that the MAIC is also not reflective of the licensed indication for siponimod in active SPMS and has limitations and areas of uncertainty. The company MAIC (included in the CS) adjusts for differences between studies owing to the companies access to IPD, however this data was not provided to the ERG for full appraisal. The ERG consider that the exploratory ERG NMA would yield more valid results than the company NMA, because the total ITT sample as opposed to active subgroup data from EXPAND trial would be more comparable to the aggregate ITT-based data of other five trials.

1.4 Issue 4: Extrapolating the effects of treatment beyond the follow up period in the clinical trials

1.4.1.1 Issue 4 a: "Would the efficacy of siponimod be expected to diminish over time?"

The ERG have no further comment on question 4a. Please refer to the ERG response contained in the ERG TE response form.

1.4.1.2 Issue 4 b: "Would patients (who do not meet the stopping criteria described in the NHS England treatment algorithm) continue to be treated with siponimod if treatment efficacy reduces over time?"

The ERG have no further comment on question 4b. Please refer to the ERG response contained in the ERG TE response form.

1.5 Issue 5: Source of natural history data

"Is it appropriate for the model to include the possibility that during the natural course of secondary progressive MS patients may improve EDSS state?"

The ERG acknowledges the company's concerns about using transition probabilities derived from the London Ontario dataset only. However, we do have concerns about using information from the EXPAND trial supplemented with transition probabilities based on the London Ontario dataset derived by the company. First, the transition matrix derived from the London Ontario dataset alone does not allow for regressions (or reductions in disability), and disability scores for people can only worsen over time. Second, transitions based on the EXPAND trial data were collected over a 2-year time horizon, whilst information from the London Ontario study were collected over 25 years.

The ERG note that the matrix derived from the London Ontario dataset alone, is not consistent with other SPMS-SPMS matrices used in the ICER 2019 report and other technology appraisals. The ERG considers that the transition probabilities are different from previous appraisals, which raises concerns about the transition probabilities used to supplement those derived from the EXPAND trial.

In summary, and for consistency we consider the transition probabilities derived from the London Ontario dataset only to be used in the economic model.

1.6 Issue 6: Treatment discontinuation

"Which of the estimates of the number of patients remaining on treatment is more plausible?"

The ERG agrees that there is an inconsistency in reporting the percentage of people remaining on treatment based on an exponential parametric curve fitted to discontinuation data, and reporting the results based on the time-dependent percentages instead of reporting those based on the time-constant discontinuation rates (see Table 5).

Table 5. Proportion of patients remaining on treatment using different treatment discontinuation models

Cycle	Proportion of patients on treatment (%)		
	Time-dependent Weibull	**Time-dependent Exponential**	**Time-constant Exponential**
0	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]
20	[redacted]	[redacted]	[redacted]
25	[redacted]	[redacted]	[redacted]
30	[redacted]	[redacted]	[redacted]
35	[redacted]	[redacted]	[redacted]
40	[redacted]	[redacted]	[redacted]
45	[redacted]	[redacted]	[redacted]
50	[redacted]	[redacted]	[redacted]

In consultation with one of our clinical advisors, our preference is to use the exponential curve fitted to the discontinuation data with time-dependent discontinuation rates. Given this change, with all other assumptions remaining unchanged, will result in a revised ERG base-case result.

The ERG's base-case analysis includes making the following changes simultaneously in the economic model for the comparison between interferon β-1b versus siponimod:

- ERG's NMA results for 6-month CDP (HR=0.80, 95% CI:0.57, 1.13) and ARR (HR=0.65, 95% CI:0.46, 1.04)
- Natural history transition probabilities based on the London Ontario dataset derived by the company
- Exponential distribution fitted to discontinuation data, with time-dependent discontinuation rates
- Treatment effect for siponimod compared to interferon β-1b applied as a rate as opposed to a probability
- Health state utility values obtained from Orme et al, 2007
- Costs of £35 for genotyping borne by the company
- Health state management costs obtained from TA320.

The ERG's base-case analysis compares siponimod versus interferon β-1b. Table 6 shows that treatment with siponimod was more costly and more effective than interferon β-1b, with an ICER of approximately [redacted] per QALY.

Table 6. ERG's base-case deterministic results, under PAS prices

Treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Interferon β-1b	[redacted]	15.58	1.06	-	-	-	-
Siponimod	[redacted]	15.66	1.43	[redacted]	0.07	0.3700	[redacted]

ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALYs, quality adjusted life-years; SPMS, secondary progressive multiple sclerosis

1.7 Issue 7: Utility values

"Which health state utility values are more plausible? EXPAND supplemented by Orme et al. or Orme et al. alone?"

The company stated that they prefer utility values from the EXPAND trial supplemented by utility values obtained from Orme et al. (2007).[12]

The ERG has provided justification as to why we considered the health state utility values obtained from Orme et al. (2007) alone to be more plausible. First, Orme et al. included more participants across all EDSS health states compared to those in the EXPAND trial. In the trial there were few participants with EDSS 0,1,2,8 and 9. Thus, the utility values derived may not be representative of people with SPMS in these health states. Second, for consistency with previous NICE technology appraisals. The Orme et al. (2007) health state utility values have been used in previous NICE technology appraisals.

1.8 ERG Replication of the company's ICERs

Table 7 reports the results based on the following assumptions reported in the TE report and some of the ERG's preferred assumptions:

- Natural history transition probabilities derived from the EXPAND trial, supplemented with transition probabilities based on the London Ontario dataset derived by the company
- No waning of the treatment effect
- Utility values from EXPAND, supplemented with values obtained from Orme et al. (2007)
- Exponential parametric curve fitted to the discontinuation data and time-constant discontinuation rates
- Treatment effect for siponimod compared to interferon β-1b (Extavia) applied as a rate as opposed to a probability
- Costs of £35 for genotyping borne by the company
- Health state management costs obtained from TA320.

This analysis used the treatment efficacy derived from the company's MAIC in an active SPMS population. Under these assumptions, the ICER for siponimod compared to interferon β-1b is approximately [redacted] per QALY.

Table 7. Cost-effectiveness results based on technical team's preferred assumptions

Model Settings	*Incremental costs*	*Incremental QALYs*	ICER
Technical Report: Technical Team's preferred assumptions as presented in the Technical Report: ERG base case + 1–3, efficacy from "company MAIC" NB: this model used time-constant discontinuation instead of the Technical Team's expressed preference for the exponential curve for time-dependent discontinuation	[redacted]	***1.67***	[redacted]

ERG; Evidence Review Group, ICER; incremental cost-effectiveness ratio, MAIC; matching-adjusted indirect comparison, NMA; network meta-analysis, PAS; Patient Access Scheme, QALY; quality-adjusted life year

Table 8 reports the results for the company's revised base-case, which were based on the following assumptions:

- Natural history transition probabilities derived from the EXPAND trial, supplemented with transition probabilities based on the London Ontario dataset derived by the company
- No waning of the treatment effect
- Utility values from EXPAND, supplemented with values obtained from Orme et al. (2007)
- Exponential parametric curve fitted to the discontinuation data and time-dependent discontinuation rates
- Treatment effect for siponimod compared to interferon β-1b (Extavia) applied as a rate as opposed to a probability
- Costs of £35 for genotyping borne by the company
- Health state management costs obtained from TA320.

These results show the ICER for siponimod compared to interferon β-1b (Extavia) is approximately [redacted] per QALY.

Table 8. Company's revised base-case

Model Settings	Incremental costs	Incremental QALYs	ICER
Revised base case: Technical Report model above + Corrected to use exponential curve for time-dependent discontinuation, as intended by Technical Team Discontinuation as a proxy for waning (Novartis revised base case for Technical Engagement)	[redacted]	***1.30***	[redacted]

ERG; Evidence Review Group, ICER; incremental cost-effectiveness ratio, MAIC; matching-adjusted indirect comparison, NMA; network meta-analysis, PAS; Patient Access Scheme, QALY; quality-adjusted life year

The company undertook two scenario analyses. The first scenario analysis applied a 50% waning of the treatment effect from Year 11 onwards and used the company's revised base-case assumptions. The results in Table 9 show that the ICER is approximately [redacted] per QALY.

Table 9. Cost-effectiveness results for treatment waning scenario (scenario 1)

Model Settings	Incremental costs	Incremental QALYs	ICER
Scenario 1: Novartis revised base case for Technical Engagement +50% waning from year 11 (aligns with NICE MTA assumption)	[redacted]	***1.21***	[redacted]
ERG; Evidence Review Group, ICER; incremental cost-effectiveness ratio, MAIC; matching-adjusted indirect comparison, NMA; network meta-analysis, PAS; Patient Access Scheme, QALY; quality-adjusted life year			

The second scenario analysis used the company's revised assumptions and applied a 25% waning of the treatment effect from Year 7, then a 50% waning of the treatment effect from Year 10 onwards. The results in Table 10 show that the ICER is approximately [redacted] per QALY.

Table 10. Cost-effectiveness results for treatment waning scenarios (scenario 2)

Model Settings	Incremental costs	Incremental QALYs	ICER
Scenario 2: Novartis revised base case for Technical Engagement +25% waning from year 7 then 50% waning from year 10 (tapered waning after 6-year extension data)	[redacted]	***1.14***	[redacted]
ERG; Evidence Review Group, ICER; incremental cost-effectiveness ratio, MAIC; matching-adjusted indirect comparison, NMA; network meta-analysis, PAS; Patient Access Scheme, QALY; quality-adjusted life year			

Summary

Using the revised model submitted by the company, the ERG was able to reproduce the ICERs reported by the company. To our knowledge, the scenario analyses, which allows for waning of the treatment effect has been implemented appropriately in the economic model.

2 REFERENCES

2. Kappos L, Bar-Or A, Cree BAC, Fox RJ, Giovannoni G, Gold R, *et al.* Siponimod versus placebo in secondary progressive multiple sclerosis (EXPAND): a double-blind, randomised, phase 3 study. *Lancet* 2018;**391**(10127):1263-73. http://dx.doi.org/10.1016/s0140-6736(18)30475-6

4. Kapoor R, Ho PR, Campbell N, Chang I, Deykin A, Forrestal F, *et al.* Effect of natalizumab on disease progression in secondary progressive multiple sclerosis (ASCEND): a phase 3, randomised, double-blind, placebo-controlled trial with an open-label extension. *Lancet Neurol* 2018;**17**(5):405-15. http://dx.doi.org/10.1016/s1474-4422(18)30069-3

5. SPECTRIMS MS Study Group. Randomized controlled trial of interferon- beta-1a in secondary progressive MS: Clinical results. *Neurology* 2001;**56**(11):1496-504.

6. Li DK, Zhao GJ, Paty DW. Randomized controlled trial of interferon-beta-1a in secondary progressive MS: MRI results. *Neurology* 2001;**56**(11):1505-13.

7. 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.

8. European Study Group. 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* 1998;**352**(9139):1491-7.

9. Kappos L, Polman C, Pozzilli C, Thompson A, Beckmann K, Dahlke F. Final analysis of the European multicenter trial on IFNbeta-1b in secondary-progressive MS. *Neurology* 2001;**57**(11):1969-75.

10. Cohen JA, Cutter GR, Fischer JS, Goodman AD, Heidenreich FR, Kooijmans MF, *et al.* Benefit of interferon beta-1a on MSFC progression in secondary progressive MS. *Neurology* 2002;**59**(5):679-87.

12. Orme M, Kerrigan J, Tyas D, Russell N, Nixon R. The effect of disease, functional status, and relapses on the utility of people with multiple sclerosis in the UK. *Value Health* 2007;**10**(1):54-60. http://dx.doi.org/10.1111/j.1524-4733.2006.00144.x

Appendix 1: NICE DSU TSD 18, section 4.2.8 Reporting of population-adjusted analyses

According to 4.2.8 of NICE TSD 18 (page 65/66), when reporting population-adjusted analyses, seven points should be addressed explicitly. We highlight below what was, and was not presented in the CS MAIC.

Point One

What the company provided:

- Variables available in each study

What the company did not provide:

- The distribution of variables available in each study represented visually
- Assessment of covariate overlap, such as comparing 95% confidence intervals, between studies
- Number of individuals assigned zero weighting (distribution of the weighting was provided as a histogram in the CQ, but the actual number of those assigned zero was not, and may be difficult to estimate the exact number based off the figures only)

Point Two

What the company provided:

- Imbalance between the study populations

What the company did not provide:

- Evidence of effect modifier status (this was assessed using univariate regression models for only 2 out of the 4 reported outcomes, not all outcomes, and the figures provided conclude that there were no statistically significant evidence of effect modifier status for the covariates identified as such in the CS)
- Proposed size of interaction effect of the EMs
- Resulting potential bias compared with a standard indirect comparison

Point Three

What the company provided:

- Distribution of weights (in CQs)
- Presentation of ESS

What the company did not provide:

- N/A

Point Four

What the company provided:

- Measures of uncertainty for any/all estimates

What the company did not provide:

- Robust sandwich estimator (covariate matrix), to provide estimates of standard errors

Point Six

What the company provided:

- Estimates for the appropriate target population using the shared effect modifier assumption

What the company did not provide:

- Comment on the representativeness of the aggregate population to the true population

Point Seven

What the company provided:

- N/A

What the company did not provide:

- A standard indirect comparison estimate should be presented alongside the population-adjusted indirect comparison, in order to convey some clarity about the impact of any population adjustment.