**National Institute for Health and Care Excellence**

**Health Technology Evaluation**

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

**Response to stakeholder organisation comments on the draft remit and draft scope**

**Please note:** Comments received in the course of consultations carried out by NICE 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 submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

**Comment 1: the draft remit and proposed process**

| **Section** | **Stakeholder** | **Comments [sic]** | **Action** |
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| Appropriateness of an evaluation and proposed evaluation route | Biogen Idec Ltd | There is an unmet need for patients with highly active relapsing-remitting multiple sclerosis (RRMS) after at least one disease modifying therapy, it is therefore appropriate for this topic to be evaluated and aligned with NICE process guidelines, appropriate to do so via a multiple technology appraisal | Thank you for your comment. No action needed. |
| MS Society | We agree that NICE should appraise the clinical and cost effectiveness of natalizumab such that it can be appraised within its full current marketing authorisation. We also agree that it is appropriate that NICE evaluate this technology through its Multi Technology Appraisal process. | Thank you for your comment. No action needed. |
| NHS England | None | No action needed. |
| Novartis Pharmaceuticals UK Ltd | We understand biosimilar medicines are not eligible to be considered for a NICE technology appraisal if the branded version is recommended. As NICE TA127 recommends natalizumab for patients as an option for rapidly evolving severe relapsing-remitting multiple sclerosis (RES), the topic ID6369 would not be prioritised for assessment. | Thank you for your comment. [NICE’s position statement on biosimilar technologies](https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/technology-appraisal-guidance/biosimilar-technologies-nice-position-statement) states that  “Biosimilars will only be appraised together with the reference products as part of a Multiple Technology Appraisal. Biosimilars will not be considered in a technology appraisal separately from the reference product.”. So, a multiple technology appraisal is appropriate for this topic. |
| Sandoz Ltd | Sandoz agrees that it is appropriate and timely to evaluate this topic. Please see our response to ‘Timing issues’. Regarding the proposed evaluation route, a multiple technology appraisal seems the best-suited methodology given the need to consider natalizumab biosimilar (Tyruko) and the originator natalizumab (Tysabri). As the biosimilar licence holder, it is important that Sandoz is able to take part in the appraisal as a Company Consultee in order to represent natalizumab biosimilar.  While beyond the terms of this appraisal, we would welcome NICE developing a methodology specifically for biosimilar medicines on account of the potential for greater health gain from off-patent biologic medicines or indications for which there is an optimised, negative or no appraisal. A proportionate approach could unlock cost-effective health gain from these medicines.  Regarding the nature of the evaluation, Sandoz considers that a **cost comparison framework** would represent a proportionate approach to this appraisal. As discussed below, the most relevant clinical comparators to natalizumab are ocrelizumab and ofatumumab. A comprehensive systematic literature review and network meta-analysis (NMA) of disease-modifying therapies (DMTs) in relapsing multiple sclerosis, published in 2023, demonstrated comparable efficacy of natalizumab, ocrelizumab and ofatumumab on outcomes of annualised relapse rate and six month confirmed disability progression.1 This is consistent with the MS Decision Aid published by the MS Trust, which categorises DMTs into ‘moderately effective’, ‘more effective’ and ‘highly effective’ based on broad categories recommended in guidelines from the Association of British Neurologists (ABN): natalizumab, ocrelizumab and ofatumumab (as well as alemtuzumab) are the only DMTs categorised as ‘highly effective’.  The highly active subgroup of relapsing-remitting multiple sclerosis (RRMS) is a subgroup borne of historical considerations of unmet need and appropriate populations for balancing benefit and risk of new treatments in the licensing of natalizumab in 2007, rather than because it represents a clinical subgroup that is expected to be a treatment effect modifier relative to the RRMS population as a whole (see Page 30 of the European Medicines Agency [EMA] Tysabri scientific discussion document).2  Generalising the evidence from whole trial NMAs into the ‘highly active’ subgroup was accepted by the Evidence Review Group (ERG) and NICE Committee in the 2021 appraisal of ofatumumab, see paragraph 3.6 of TA699.3 Based on the expected comparable effectiveness of natalizumab, ocrelizumab and ofatumumab in RRMS – and by extension ‘highly active’ RRMS – a cost comparison would represent a proportionate approach to this evaluation. | Thank you for your comment. [NICE’s position statement on biosimilar technologies](https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/technology-appraisal-guidance/biosimilar-technologies-nice-position-statement) states that  “Biosimilars will only be appraised together with the reference products as part of a Multiple Technology Appraisal. Biosimilars will not be considered in a technology appraisal separately from the reference product.”. So, a multiple technology appraisal is appropriate for this topic. |
| Merck Serono | No comments | Thank you for your comment. No action needed. |
| Wording | Biogen Idec Ltd | The wording is appropriate but for accuracy the brand name for natalizumab biosimilar should be in parentheses rather than the non-propriety name as follows:  “To appraise the clinical and cost effectiveness of natalizumab (Tysabri) and natalizumab biosimilar (Tyruko) within its marketing authorisation for treating highly active relapsing-remitting multiple sclerosis after at least one disease modifying therapy.” | Thank you for your comment. The wording of the remit has been amended as requested. |
| MS Society | The wording of the remit reflects the issues of clinical and cost effectiveness that NICE should consider.  An MS Society funded project that aimed to understand DMT treatment decisions from the perspective of people with relapsing remitting MS, the CRIMSON review, indicated that mode of delivery plays a role in decisions not to start, or to delay at DMT, or in which DMTs to take. It is important that eligible patients have access to all available treatment formats including subcutaneous and intravenous options and this is reflected in the remit and scope. | Thank you for your comment. NICE will appraise the technology within its marketing authorisation, considering any clinical or cost evidence presented. No action needed. |
| NHS England | None | No action needed. |
| Novartis Pharmaceuticals UK Ltd | Could you please provide clear guidance on the intended population of patients natalizumab is recommended or not recommended in as the current wording ‘people with highly active disease’ is not very well defined. | The wording of the population has been kept broad to align with other scopes in relapsing remitting MS. No action needed. |
| Sandoz Ltd | Yes, the wording of the remit is appropriate. | Thank you for your comment. No action needed. |
| Merck Serono | No comments | Thank you for your comment. No action needed. |
| **Timing issues** | Biogen Idec Ltd | The proposed timelines are appropriate | Thank you for your comment. No action needed. |
| MS Society | We believe that NICE should prioritise the publication of this appraisal to support the prescribing of natalizumab within its licensed indication on the NHS in England, and to support the effective use of a biosimilar product.  The wider population of people with highly active disease despite treatment with at least one disease modifying therapy would benefit from a highly effective alternative treatment option. | Thank you for your comment. NICE aims to provide draft guidance to the NHS as close as possible to the date when the marketing authorisation for a technology is granted. NICE has scheduled this topic into its work programme. No action needed. |
| NHS England | None | No action needed. |
| Novartis Pharmaceuticals UK Ltd | None | No action needed. |
| Sandoz Ltd | We consider this evaluation to be a high priority given:   * The changes in treatment landscape and the availability of further clinical evidence for natalizumab since TA127 was published in 2007, including real-world evidence from countries in which natalizumab is reimbursed for its full licensed population. This requires an updated evaluation of natalizumab and natalizumab biosimilar in patients with highly active RRMS after at least one DMT * The clinical importance to patients of timely access to high efficacy DMTs , as supported by the MS Needs report and a consensus statement published in 2022.4, 5 During the COVID-19 pandemic, NHS England took the decision to expand use of natalizumab to include all patients within its licence.6 A 46.9% increase in initiation of natalizumab was seen in 2020 relative to 2019, supporting the desire among clinicians to be able to use natalizumab within its broader licensed population beyond the current NICE restriction7 * The availability of natalizumab biosimilar and the associated impact on the assessment of cost-effectiveness of natalizumab. Biological medicines are currently the largest cost and cost growth areas in the NHS medicines budget;8 as such, “using best value biologic medicines in line with NHS England commissioning recommendations" is one of NHS England’s sixteen national medicines optimisation opportunities for the NHS in 2023/2024.9 Natalizumab biosimilar supports the potential identified by the NHS to deliver savings of up to £300m each year through use of biosimilars, enabling more patients to have access to other life-saving and life-enhancing treatments.8 Reports from the NHS Long-Term Plan have demonstrated the value that driving uptake of biosimilars can provide in terms of cost-savings and opportunities for reinvestment10 | Thank you for your comment. NICE aims to provide draft guidance to the NHS as close as possible to the date when the marketing authorisation for a technology is granted. NICE has scheduled this topic into its work programme. No action needed. |
| Merck Serono | No comments | Thank you for your comment. No action needed. |
| Additional comments on the draft remit | Biogen Idec Ltd | None | No action needed. |
| MS Society | None | No action needed. |
| NHS England | None | No action needed. |
| Novartis Pharmaceuticals UK Ltd | None | No action needed. |
| Sandoz Ltd | N/A | Thank you for your comment. No action needed. |
| Merck Serono | None | Thank you for your comment. No action needed. |

Comment 2: the draft scope

| **Section** | **Consultee/ Commentator** | **Comments [sic]** | **Action** |
| --- | --- | --- | --- |
| Background information | Biogen Idec Ltd | The background information is accurate and complete | Thank you for your comment. No action needed. |
| MS Society | The background information is accurate and complete. | Thank you for your comment. No action needed. |
| NHS England | None | No action needed. |
| Novartis Pharmaceuticals UK Ltd | Could you please provide clear guidance on the intended population of patients natalizumab is recommended or not recommended in as the current wording ‘people with highly active disease’ is not very well defined. | The wording of the population has been kept broad to align with other scopes in relapsing remitting MS. No action needed. |
| Sandoz Ltd | Sandoz agrees with the overall content of the background information, and suggest the following two amendments are made to improve the clarity and accuracy of the content:   * The TA number (TA706) accompanying the bullet point “ponesimod and ofatumumab for active RRMS” is incorrect. TA706 is for ozanimod which is not recommended by NICE for patients with active RRMS; the correct TA numbers are TA767 for ponesimod, and TA699 for ofatumumab * The draft scope states that MS is a “neurological condition which affects the brain, optic nerves, and spinal cord.” While Sandoz agrees that this is not factually incorrect, the current wording feels somewhat restrictive, as MS is a condition that can affect all cranial nerves. Sandoz requests that the wording is updated to a “neurological condition which affects the brain and spinal cord” to broaden this point | Thank you for your comment. The scope has been updated as requested. |
| Merck Serono | No comments | Thank you for your comment. No action needed. |
| Population | Biogen Idec Ltd | The population is appropriately defined | Thank you for your comment. No action needed. |
| MS Society | The population is defined appropriately. | Thank you for your comment. No action needed. |
| NHS England | None | No action needed. |
| Novartis Pharmaceuticals UK Ltd | - | No action needed. |
| Sandoz Ltd | The focus of this evaluation should be on appraising the case for extending the recommendation for natalizumab to cover the part of its current licence in which it is not currently recommended by NICE.  Following the update to the licence wording for natalizumab in 2016, this population is ‘patients with highly active disease despite a full and adequate course of treatment with at least one disease modifying therapy (DMT)’. A positive recommendation for this population would make access to natalizumab in England and Wales consistent with the recommendation for natalizumab in current European and ABN guidelines; both guidelines recommend natalizumab for use in active RRMS, without restriction to rapidly evolving severe disease only.11, 12  Therefore, Sandoz agrees with the population defined in the draft scope: ‘patients with highly active disease despite a full and adequate course of treatment with at least one disease modifying therapy’. We note that the marketing authorisation wording for natalizumab refers to a ‘full and adequate course’ of treatment with at least one DMT but understand that the NICE-defined population encompasses this patient population definition and that NICE will appraise natalizumab within the terms of its licence.  Of relevance to note for the subsequent appraisal of evidence, Sandoz wishes to highlight that, in clinical practice, different forms of MS are often not clearly defined and are instead considered to be part of a wider disease spectrum. As such ‘highly active’ disease is not constrained by a strict definition in clinical practice; varying definitions of the ‘highly active’ subgroup have been used previously, reflecting the specific regulatory wording of the appraised treatments. For example, previous appraisals in this indication have utilised varied criteria relating to previous relapses and lesions on magnetic resonance imaging (MRI). In clinical practice, Sandoz understands the preference among clinicians is to maintain a broad definition of highly active disease, enabling clinician discretion to determine whether a patient classifies as ‘highly active’ or ‘active’. This is reflected in the discussion at Committee meetings of prior NICE appraisals in MS. For example, the Final Appraisal Determination document for ponesimod notes the following with regards to discussion of the highly active disease subgroup: ‘The clinical experts considered that the different forms of multiple sclerosis are part of a disease spectrum rather than having clearly defined aspects’.13 In this context, we agree with the NICE draft scope population wording as it aligns to the natalizumab licence and avoids imposing an overly specific definition for a population that does not operate by a strict definition in clinical practice. | Thank you for your comment. No action needed. |
| Merck Serono | No comments | Thank you for your comment. No action needed. |
| Subgroups | Biogen Idec Ltd | N/A the population as defined is already a subgroup of the broader highly active RRMS population | Thank you for your comment. No action needed. |
| MS Society | n/a | Thank you for your comment. No action needed. |
| NHS England | None | No action needed. |
| Novartis Pharmaceuticals UK Ltd | - | Thank you for your comment. No action needed. |
| Sandoz Ltd | Sandoz agrees that there are no relevant subgroups to consider within this appraisal. | Thank you for your comment. No action needed. |
| Merck Serono | No comments | Thank you for your comment. No action needed. |
| Comparators | Biogen Idec Ltd | The comparators are inappropriately defined in the draft scope. Biogen believe the comparators should be as follows (consistent with recent prior appraisals in this therapeutic area e.g. TA676, TA699, TA616 and TA533:   * Fingolimod * Cladribine tablets * Ocrelizumab * Alemtuzumab * Ofatumumab * Ponesimod   Dimethyl fumarate, diroximel fumarate and teriflunomide all have statements in their respective NICE recommendations as follows:  “recommended as an option for treating adults with active relapsing‑remitting multiple sclerosis (normally defined as 2 clinically significant relapses in the previous 2 years), only if they do not have highly active or rapidly evolving severe relapsing‑remitting multiple sclerosis and  This statement would therefore exclude these treatments from use in this population under appraisal.  Whilst the beta interferons and glatiramer acetate have marketing authorisations for broad RRMS, they are seldom used for patients with breakthrough disease activity whilst receiving a full and adequate course of another disease modifying therapy (DMT). When these treatments infrequently used for this population, it is generally a patient/ clinician preference, trading superior efficacy for a more favourable safety profile.  2) The comparator section is also overly complex  For the remaining sub-populations specified in the draft scope (“for people with disease activity after 2 DMTs” and “for people with disease activity after 1 or 2 DMTs”) none of the listed comparators have a stipulation of two DMTs in their respective marketing authorisations or NICE guidance.  The distinction between number of prior DMTs should therefore be removed and the included comparators consolidated into a single group. | Thank you for your comment. Dimethyl fumarate, diroximel fumarate and teriflunomide have been removed from the scope The committee will consider the most appropriate comparators for this technology. Therefore, all other comparators (even those rarely used in this population) remain in the scope. |
| MS Society | The listed comparators are considered the standard NICE approved treatments used in the NHS, and all relevant NICE approved comparators have been included.  In addition, autologous haematopoietic stem cell transplantation is sometimes provided by the NHS as a DMT for select patients with highly active relapsing MS. | Thank you for your comment. Autologous haematopoietic stem cell transplantation has been added to the scope as a relevant comparator. |
| NHS England | None | No action needed. |
| Novartis Pharmaceuticals UK Ltd | The current presentation of DMTs in this section is slightly misleading as most DMTs listed in the comparator section can be used for RRMS patients with active disease as a first line and/or second line therapy. It may be clearer to the reader if the treatments were all grouped under one section.  In addition, whilst NICE recommends fumerates for ‘active RRMS’ it specifically indicates that fumerates should not be used in patients with ‘highly active MS or rapidly evolving severe RRMS’: considering the intended population for this application, we suggest to remove fumerates from the DMT list (please refer to NICE guidelines for TA794 & TA320). | Thank you for your comment. Dimethyl fumarate, diroximel fumarate and teriflunomide have been removed from the scope. The committee will consider the most appropriate comparators for this technology. Therefore, all other comparators (even those rarely used in this population) remain in the scope. |
| Sandoz Ltd | MS is a complex and fundamentally unpredictable condition; choice of treatment is highly dependent on each patient and their individual circumstances.  Natalizumab is a monoclonal antibody DMT classed as a drug of high efficacy (average relapse reduction substantially more than 50%) as per ABN guidelines.12 Natalizumab would therefore be used in patients for whom a high efficacy biologic treatment is considered the most appropriate treatment approach on the balance of benefit:risk in the context of the patient need. This is reflected in ABN guidelines, which state that “alemtuzumab and natalizumab are appropriate where individuals and their multiple sclerosis specialist neurologists are most concerned to achieve high efficacy, despite the more complex safety profile compared to Category 1 drugs”.12  Alternative licensed high-efficacy biologic treatments other than natalizumab are ocrelizumab and ofatumumab (both licensed after the 2015 ABN guidelines were published) and alemtuzumab; therefore, these represent the treatment options that would represent the most relevant treatment choice alternatives to natalizumab in clinical practice. However, alemtuzumab is associated with a specific and complex safety profile that has restricted its use in UK clinical practice, and Sandoz understands that alemtuzumab has limited usage in practice as a treatment option among patients with ‘highly active’ RRMS.14, 15 As such, ofatumumab and ocrelizumab represent the most relevant comparators to natalizumab for patients with highly active disease after at least one DMT.  The other comparator treatments listed in the draft scope are not relevant comparators in clinical practice as they are not ‘high efficacy’ biologic treatments and would therefore generally be used in a different patient-specific clinical context to natalizumab. | Thank you for your comment. Dimethyl fumarate, diroximel fumarate and teriflunomide have been removed from the scope. The committee will consider the most appropriate comparators for this technology. Therefore, all other comparators (even those rarely used in this population) remain in the scope. |
| Merck Serono | The ‘Comparators’ section lists cladribine only as a comparator for people with disease activity after 2 DMTs, and states that cladribine is still ‘subject to NICE evaluation’.  This is incorrect as cladribine is not subject to NICE evaluation in highly active RRMS. Cladribine is recommended as an option for treating highly active MS in adults if the person has RRMS that has responded inadequately to treatment with disease-modifying therapy (defined as 1 relapse in the previous year and MRI evidence of disease activity). This recommendation was published in 2019 (TA616).  Cladribine is only subject to NICE evaluation in the broader active RRMS population (ID6263).  Also, it is not clear why cladribine is only listed as a comparator for people with disease activity after 2 DMTs. This requirement for previous treatment with 2 DMTs is not specified in the NICE recommendation for cladribine (TA616). The recommendation only refers to “RRMS that has responded inadequately to treatment with DMT” and does not include a specific number of DMTs.  To avoid confusion, we propose that the ‘Comparator’ section is updated to align with the scoping documents in previous MS appraisals. Below is the list comparators we believe should be listed here as these DMTs are recommended in highly active RRMS/or active RRMS including highly active subgroups:  For people with highly active relapsing-remitting multiple sclerosis despite previous treatment:  • cladribine tablets  • alemtuzumab  • fingolimod  • ocrelizumab  • ofatumumab  • ponesimod  • glatiramer acetate  • interferon beta-1a  • interferon beta-1b | Thank you for your comment. The scope has been amended to remove thar cladribine is under NICE appraisal. Dimethyl fumarate, diroximel fumarate and teriflunomide have been removed from the scope. The committee will consider the most appropriate comparators for this technology. Therefore, all other comparators (even those rarely used in this population) remain in the scope. |
| Outcomes | Biogen Idec Ltd | The listed outcomes are appropriate | Thank you for your comment. No action needed. |
| MS Society | During the course of the appraisal, it will be important to consider the potential effects of the recommendations on the ability of people with MS to remain in work and engage with wider society, and the potential impact on carers.  These outcomes can be difficult to capture with standard validated measures. However, they can be assessed through further engagement with patients and patient charities. | Thank you for your comment. The highlighted outcomes will be captured in ‘health-related quality of life’ which is currently listed as an outcome in the scope. |
| NHS England | None | No action needed. |
| Novartis Pharmaceuticals UK Ltd | Brain volume loss’ is widely used as a robust outcome indicator in recent trials, as it provides a reliable comparison of neuroprotective potential of DMTs, we therefore suggest this is included as an outcome.  Considering the increased risk of PML associated with nataluzimab and in particular with prolonged use of nataluzimab, we suggest to include this and the subsequent suggested JCV testing and MRI screening in the ‘adverse events of treatment’ outcome. | Thank you for your comment. Brain volume loss will be captured in the currently listed outcomes ‘symptoms of multiple sclerosis’ and ‘disease progression’. Other highlighted outcomes will be captured under the currently listed outcome of ‘adverse effects of treatment’. No action needed. |
| Sandoz Ltd | The outcomes listed are considered appropriate, although Sandoz recommends that patient reported outcomes (i.e. the fatigue severity score or SF-36) are added to the listed outcomes to ensure the aspects of MS disease activity and impact on patients are more comprehensively captured during this evaluation. | Thank you for your comment. The scope has been kept broad to include the main outcomes that are relevant to estimating clinical effectiveness. No action needed. |
| Merck Serono | No comments | Thank you for your comment. No action needed. |
| Equality | Biogen Idec Ltd | One of the known drivers of health inequalities is distance from a treatment centre, particularly for those people who travelling is difficult, or have more limited access to transport. Tysabri SC has the potential to move closer to home and therefore reduce health inequalities  As Tysabri SC is quicker to administer & monitor post dosing, there is a time saving for patients which can reduce time off work, childcare fees etc. These time and cost savings will be increased if services are set up closer to patient homes so that patients travel time and costs are reduced. A multicentre UK study showed that 52.1% of patients have a travelling time of greater than one hour to obtain treatment.1  1. Mills et al. Natalizumab treatment satisfaction in the TONIC-MS study: Latest results. Association of British Neurologist 2023. 9-12 May, Belfast. | Thank you for your comment. Please see the accompanying EIA for further details. The committee will consider equalities issues where evidence is presented. No change to scope required. |
| MS Society | The following equality considerations may apply to the NICE MTA.  MS affects two to three times as many women as men. Any NICE recommendation that resulted in fewer available treatment options for the wider population of people with highly active relapsing MS is likely to have a disproportionate effect on women.  A decision by NICE not to recommend natalizumab for the wider population of people with highly active relapsing MS may have a disproportionate impact on younger people, who are more likely to consider family planning in their treatment decisions. Natalizumab offers fewer restrictions on family planning compared to some other DMTs. | Thank you for your comment. Please see the accompanying EIA for further details. The committee will consider equalities issues where evidence is presented. No change to scope required. |
| NHS England | The current remit and scope does not address the needs of women with RRMS. In particular, women who are planning pregnancy or who are pregnant who may need to start or switch to treatment with natalizumab.  Pregnancy is a protected characteristic. MS is more common in females, and we estimate that around 600 women with MS become pregnant in the UK each year. The needs of these women are currently not represented in NICE TAs, taking into account the range of MS DMT available and considerations around those that are safe to continue into pregnancy.  Pregnant women and women planning pregnancy with relapsing remitting multiple sclerosis and those with disease activity on first line therapy currently have to switch back to a less effective DMT (platform injectable treatments such as beta interferon, glatiramer acetate, or stop DMT) as oral DMTs are in general contraindicated for use in pregnancy, and S1P inhibitors (fingolimod, ponesimod) are teratogenic and so must be washed out prior to pregnancy. This particularly affects the population who do not meet the criteria for RES-MS and so cannot access natalizumab.  The remit and scope must specifically include and examine the evidence to support access to natalizumab treatment for women with active/highly active RRMS who are planning pregnancy or who are pregnant. In general, pregnancy studies stratify by DMT exposure rather than by level of disease activity prior to DMT initiation. Focusing the scope on definitions of disease activity therefore excludes potential evidence of benefit of natalizumab/natalizumab biosimilar in a population with a protected characteristic.  This leads to inequity within the MS population with the potential for avoidable relapses and longer term disability, where those who are not planning pregnancy can remain on more effective treatments, whereas those planning pregnancy are forced to switch to less efficacious treatments | Thank you for your comment. Please see the accompanying EIA for further details. The committee will consider equalities issues where evidence is presented. No change to scope required. |
| Novartis Pharmaceuticals UK Ltd | - | Thank you for your comment. No action needed. |
| Sandoz Ltd | Certain sub-populations of patients with highly active RRMS face a lack of efficacious treatment options; such patients include immunocompromised individuals and women of childbearing potential.  Immunocompromised patients  Sandoz acknowledges that the Summary of Product Characteristics (SmPC) for natalizumab states that natalizumab is contraindicated for ‘patients with increased risk for opportunistic infections, including immunocompromised patients’.  However, Sandoz highlights that during the early phases of the COVID-19 pandemic, the ABN issued guidance on the use of DMTs in MS in response to the pandemic; a context in which the role of DMTs in increasing patient risk of infection was an important consideration. These guidelines viewed natalizumab as the safest high-efficacy therapy available for patients with MS in this context.6  Women of childbearing potential  The natalizumab SmPC states that use of natalizumab during pregnancy should be based on a benefit/risk evaluation accounting for the patient’s clinical condition and possible return of disease activity with discontinuation.16 Natalizumab should be used during pregnancy only if clearly needed.16 UK consensus guidelines for the treatment of MS in pregnancy (released in 2019 in collaboration with the ABN MS Advisory Group) advised that natalizumab is the only highly effective biologic treatment suitable for use during pregnancy.17 According to the guidelines, pregnancy is not recommended for four months following alemtuzumab and for 12 months after receiving ocrelizumab (ofatumumab had not yet received marketing authorisation in the EU by 2019 and therefore was not considered during the development of these guidelines).17 | Thank you for your comment. Please see the accompanying EIA for further details. The committee will consider equalities issues where evidence is presented. No change to scope required. |
| Merck Serono | No comments | Thank you for your comment. No action needed. |
| Other considerations | Biogen Idec Ltd | Section 5.1 of the SmPC for Tysabri contains data on the efficacy when used with extended interval dosing (EID) compared to the standard dosing. Biogen have data on the percentage of patients receiving EID in the UK and believe that it is this dosing regimen that should be considered in the evaluation  Section 4.2 Tysabri SmPC. ‘Patients treated with natalizumab must be given the patient alert card and be informed about the risks of the medicinal product (see also package leaflet). After 2 years of treatment, patients should be re-informed about the risks, especially the increased risk of Progressive Multifocal Leukoencephalopathy (PML) and should be instructed together with their caregivers on early signs and symptoms of PML’.  In order to quantify the risk of PML, Biogen provide a Stratify JCV test free of charge (includes all materials & shipping for the test) for patients being considered, or being prescribed, Tysabri IV / SC. Stratify JCV is not available to patients being prescribed Tyruko and alternative tests are not directly comparable when calculating the risk of PML. | Thank you for your comment. No action needed. |
| MS Society | None | No action needed. |
| NHS England | None | No action needed. |
| Novartis Pharmaceuticals UK Ltd | - | Thank you for your comment. No action needed. |
| Sandoz Ltd | Not applicable | Thank you for your comment. No action needed. |
| Merck Serono | No comments | Thank you for your comment. No action needed. |
| Questions for consultation | Biogen Idec Ltd | *What criteria would be used to define highly active relapsing remitting multiple sclerosis in clinical practice?*  Response:  In clinical trials, the definitions for highly actively RRMS (that is not RES) are as follows:  patients have an unchanged or increased relapse rate or ongoing severe relapses compared with the previous year despite treatment with DMT.  defined as 1 relapse in the previous year and magnetic resonance imaging (MRI) evidence of disease activity  *Where do you consider natalizumab and natalizumab biosimilar will fit into the existing care pathway for highly active relapsing remitting multiple sclerosis despite a full and adequate course of treatment with at least one disease modifying therapy?*  Response:  Treatment decisions are based on a number of clinical and patient factors including (but not limited to) the benefit/risk profile, route, frequency and setting of administration and lifestyle factors such as family planning and travel. Natalizumab and natalizumab biosimilar should be considered as a first line option for RRMS despite a full and adequate course of treatment with at least one disease modifying therapy.  *Does the current scope match the NHS treatment algorithm appropriately?*  Response:  The current comparator section listed in the draft scope does not reflect the NHS England treatment algorithm. The suggestion made by Biogen in this consultation response form does match the treatment algorithm.  *How often are beta interferons used in untreated people with highly active relapsing*  *remitting multiple sclerosis?*  Response:  See response above in the comparator section.  *What disease modifying treatments, other than beta interferons, are used in*  *untreated people with highly active relapsing remitting multiple sclerosis? Are these*  *treatments associated with different outcomes to beta interferons?*  Response:  Beta interferons are seldom used in this population, the Biogen proposed comparators are all used in the proposed population. Natalizumab and the proposed comparator list are associated with superior efficacy outcomes in both relapse rates and confirmed disability progression compared to beta interferons.1  1. Spelman T et al. Comparative Effectiveness and Cost-Effectiveness of Natalizumab and Fingolimod in Patients with Inadequate Response to Disease-Modifying Therapies in Relapsing-Remitting Multiple Sclerosis in the United Kingdom. Pharmacoeconomics. 2022 Mar;40(3):323-339. doi: 10.1007/s40273-021-01106-6. Epub 2021 Dec 18. PMID: 34921350; PMCID: PMC8866337.  *Would ofatumumab and ponesimod be used in people with highly active relapsing*  *remitting multiple sclerosis despite a full and adequate course of treatment after at*  *least one disease modifying therapy?*  Response:  Yes, as per NICE guidance and the NHS England DMT algorithm  *Would subcutaneous and intravenous formulations of natalizumab be used*  *interchangeably? If not, in whom would each formulation be used? Would the*  *comparators be different for each formulation?*  Response:  Prescribing decisions are based on a number of clinical and patient factors. Although they would have the same comparators there are number of considerations when deciding on subcutaneous (SC) and intravenous (IV) formulations including:  Patient preference: In a study comparing Tysabri SC with Tysabri IV, 87.8% of patients preferred Tysabri SC at the end of cross over study.1  Administration cost due to less staffing resource required  NHS capacity (given lower administration time of SC)  Ability to deliver SC closer to patient home (no IV suite required)  Patients with cannulation issues  Environmental impact Tysabri SC has a potential positive environmental impact when compared to Tysabri IV:  Reduced waste for incineration  Reduced electricity consumption  Reducing CO2 emissions by reducing travel times  1. Wiendl et al. Results from the NOVA extension study evaluating patient preference for subcutaneous versus intravenous administration with natalizumab Q6W dosing. 29th Congress of the European Committee for Treatment & Research in Multiple Sclerosis. October 11-13, Milan Italy.  *Would natalizumab and natalizumab biosimilar be a candidate for managed access?*  Response:  Biogen do not consider natalizumab or natalizumab biosimilar to be candidates for managed access. | Thank you for your comment. See relevant responses above. No action needed. |
| MS Society | None | No action needed. |
| NHS England | The subtyping of relapsing remitting MS into active/highly active/RES MS reflects criteria used in clinical trial inclusion criteria, rather than clinical practice. Clinical judgement around disease activity and prognostication in MS relates to a number of factors, including relapse rate, relapse site, MRI appearance (number and location of lesions), alongside factors such as age and disability level at presentation.  It is important to note that MS is commonly diagnosed in females of childbearing age, many of whom have not completed their families at diagnosis. At present, there is no consideration of pregnancy plans within MS DMT TAs, which has led to inequitable opportunity for disease control for women with active/highly active MS who are considering trying to conceive. Furthermore, patients may need to switch DMT for reasons unrelated to disease activity; family planning is one such reason. It is important that patients in such a situation are considered within TAs.  By focussing on artificial distinctions of disease activity within RRMS, which are not  DMT selection is complex, taking into account disease activity, risk considerations, patient factors – including, but not limited to family planning, and patient preference. reflected in the international literature around pregnancy planning, this inequity is inadvertently perpetuated.  Natalizumab and natalizumab biosimilar should be made available as an option for people with MS who have active disease despite a full and adequate course of at least one DMT. We recognise concerns regarding safety, however safety mitigations relating to PML risk stratification, screening and monitoring mean that it enables patients to rapidly achieve disease control in the context of breakthrough disease without substantial therapeutic lag, as may be seen with other second line DMT.  Please note that a preliminary policy proposition has been accepted onto the NHSE Specialised Services clinical commissioning policy development work programme for the topic “Natalizumab for women with RRMS who are planning pregnancy or who are pregnant”. The call for this work has come from the CRG, who recognise that there is substantial inequity in opportunity for disease control for women with MS considering pregnancy, which is a protected characteristic.  The Policy Working Group consider that natalizumab and natalizumab biosimilar should be made available to those women with RRMS who are planning pregnancy or who are pregnant who wish to receive it, irrespective of whether they were receiving no disease-modifying drug treatment or at least one disease-modifying drug treatment prior to planning pregnancy or pregnancy.  The current scope does not address the situation where women with RRMS who are planning pregnancy or who are pregnant need to access natalizumab in order to achieve or maintain disease control. The NHS treatment algorithm states that “Where pregnancy is planned or desired, people with MS should usually be offered a DMT of at least similar efficacy which is compatible with pregnancy than if this were this not a consideration. The aim should be to allow people to make an informed choice about DMT use, taking into account safety around pregnancy alongside minimising the risk of relapse in the mother” (section 4). The current scope does not match this aspiration. | Thank you for your comment. Please see the accompanying EIA for further details on identified inequalities. The committee will consider equalities issues where evidence is presented. No change to scope required. |
| Novartis Pharmaceuticals UK Ltd | Relating to the following question;  *Would ofatumumab and ponesimod be used in people with highly active relapsing remitting multiple sclerosis despite a full and adequate course of treatment after at least one disease modifying therapy?*  Ofatumumab can be used in active RRMS patients in any line. Naive or treatment experienced (NICE TA699) | Thank you for your comment. No action needed. |
| Sandoz Ltd | How often are beta interferons used in untreated people with highly active relapsing remitting multiple sclerosis?  Sandoz understands that beta interferons are seldom used in patients with highly active RRMS, given the availability of alternative, higher efficacy treatment options. This is consistent with the conclusions in the NICE appraisal of peginterferon beta-1a (NICE TA624), for which patients and clinicians stated that ‘[peginterferon beta-1a] would not be their first choice treatment for people with more severe forms of relapsing-remitting multiple sclerosis’ and that it would primarily be used as a first-line treatment or when other first-line treatments are not tolerated for RRMS (i.e. at an earlier, less severe, stage of disease).18 This appraisal did not restrict use of peginterferon beta-1a in the highly active RRMS population, acknowledging the value of patient choice and reflecting that some groups of patients, such as immunosuppressed patients and pregnant women, may remain treated with beta interferons.18 However, usage in highly active RRMS is expected to be limited and not in the context of being considered an alternative choice to natalizumab. Furthermore, the final scopes of recent appraisals within the RRMS disease landscape that have considered the highly active subgroup specifically have not included beta interferons – or indeed the other treatments listed in the “for people with disease activity after 1 DMT” section of the draft scope – as relevant comparators.19-21 Given this, Sandoz considers that the beta interferons (along with a number of the other draft scope comparators) do not represent relevant comparators to natalizumab or natalizumab biosimilar for this appraisal and recommend their removal from the scope.  Would subcutaneous and intravenous formulations of natalizumab be used interchangeably? If not, in whom would each formulation be used? Would the comparators be different for each formulation?  In UK clinical practice, patients and clinicians value choice in route of natalizumab administration, with different advantages associated with each formulation. Sandoz emphasises that, while patients may be switched from one formulation onto the other after careful consideration based on a clear rationale, subcutaneously administered (SC) and intravenously administered (IV) natalizumab should not be considered as interchangeable.  For example, a key differentiation of IV natalizumab compared to SC natalizumab is the ability to have extended interval dosing (EID) which lowers drug exposure, mitigating the risk of natalizumab-associated adverse events. A growing body of evidence demonstrates that patients with RRMS can be switched from treatment with IV natalizumab every four weeks to every 6 weeks, without any meaningful efficacy loss.22-25 EID may also be cost-saving and more convenient for patients due to fewer infusions and, in turn, reduced frequency of hospital visits.26 Notably, to Sandoz’s knowledge, no clinical data are available on either the safety or efficacy of EID with the SC route of administration.16 Indeed, based on available evidence, it was concluded in the natalizumab assessment report from the EMA that mean natalizumab trough levels are “slightly, but consistently reduced” with SC administration compared with IV administration;27 findings from the NEXT trial also demonstrate that natalizumab trough drug levels are on average 55% lower for SC administration than IV administration.28 These findings may indicate that EID with SC natalizumab would be less feasible due to the risk of reaching subtherapeutic natalizumab concentrations between doses, though Sandoz acknowledges the complexities surrounding interpretation of pharmacokinetic-pharmacodynamic relationships and the small sample sizes on which these current findings are based. In summary, the potential for EID with SC natalizumab remains to be supported to the degree that has been done for IV natalizumab.  As another example of the value of choice, Sandoz understands that, for some patients, the community aspect of receiving treatment via IV administration, involving time spent in hospital alongside others facing similar challenges, presents an added advantage.  Finally, it is important to note that the SC formulation of natalizumab was granted marketing authorisation by the EMA in April 2021 on the basis of two studies (DELIVER and REFINE).16, 29, 30 These studies are Phase 1 and Phase 2 studies, respectively. DELIVER had a primary objective to compare pharmacokinetics and pharmacodynamics and for REFINE the EMA noted that the exploratory nature of the study meant that no formal efficacy comparisons were made. Therefore, to date, the vast majority of high quality evidence for the efficacy and safety of natalizumab continues to be for the IV formulation. Published and ongoing studies for SC natalizumab are frequently limited by their small sample sizes among natalizumab SC arms and focus on pharmacokinetic and pharmacodynamic primary outcomes.31-34 | Thank you for your comment. See relevant responses above. No action needed. |
| Merck Serono | No comments | Thank you for your comment. No action needed. |
| Additional comments on the draft scope | Biogen Idec Ltd | None | No action needed. |
| MS Society | None | No action needed. |
| NHS England | None | No action needed. |
| Novartis Pharmaceuticals UK Ltd | Regarding the Related National Policy; NHS England (2019) Treatment Algorithm for Multiple Sclerosis: Disease-Modifying Therapies. There has been an update in 2023. | Thank you for your comment. The scope has been updated as requested. |
| Sandoz Ltd | Not applicable | Thank you for your comment. No action needed. |
| Merck Serono | No comments | Thank you for your comment. No action needed. |

**The following stakeholders indicated that they had no comments on the draft remit and/or the draft scope**

# Sanofi