Multiple Technology Appraisal

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

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

MULTIPLE TECHNOLOGY APPRAISAL

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

Contents:

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Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 02 April 2025. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Biogen Idec Ltd

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	Not applicable
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

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Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	The Company is concerned that the economic conclusion in the Draft Guidance doesn't take into account the potential workload savings and reduction in NHS and patient burden associated with the SC formulation of natalizumab-TYS. SC natalizumab-TYS – administered through the Tysabri Home Injection service (THIS) provided by the Company – enables care closer to home, minimises patient travel time required for treatment, helping to address inequalities and reduces patient costs and administration time (e.g., transport, childcare, lost productivity). When administered in a secondary care setting, cost savings to the NHS include reduction in HCP time, infusion chair time, and equipment costs. Increased infusion suite capacity also allows more MS patients to be treated reducing waiting lists. This was detailed in the Company's initial submission to NICE, and in subsequent communications with NICE and the EAG. The Company disagrees with the conclusion in the Draft Guidance that "the overall time saving with subcutaneous natalizumab [is] minimal". Silingardi et al. 2023 showed in a time and motion study in Salford that when administered in a secondary care setting, SC natalizumab-TYS provided DMT treatment total savings of 1 h 32 min in the SC cohort compared with IV administered cohort (see CS section B.2.6.1, pg. 55).[1] Similar time and resource saving were reported through a survey of clinicians and patients treated at Morriston Hospital, Swansea, which showed an average combined infusion and surveillance time for IV natalizumab-TYS of 142 minutes, reducing to an average of 61 minutes for SC natalizumab-TYS.[2] A model developed by the Company to estimate costs and time savings for switching from IV to SC estimates that switching 500 patients results in hospital chair time savings of [redacted], nurse/pharmacy time savings of [redacted] and total cost savings of [redacted].[3] SC also provides direct patient benefits. In the Nova (Part 2 study), the majority of patients on Q6W dosing preferred SC vs. IV and 82.9% of patients cited the key reason as "requiring less time in clinic" (see EAG report consultation response form pg. 7).[4] Similarly, the TONiC study highlighted all but one patient who switched from IV to SC expressed either a "fairly strong" or "very strong" preference for SC vs IV driven by time savings (see CS section B.2.6.1, pg. 56).[5] Survey data from Morristown Hospital, Swansea showed that 96% of the 64 patients who had switched to SC natalizumab-TYS from IV, or who initiated the SC formulation, were "satisfied" or "very satisfied" with switching. TONiC also showed that 39.8% of patients with MS travelled between 1 to 2 hours, 8% travelled 2 to 4 hours and 3.5% travelled over 4 hours for MS treatment administration, further showing the advantages of care closer to home.[5] The Tysabri Home Injection Service (THIS) provided by the Company includes delivery of natalizumab-TYS and Biogen-funded homecare nurse for administration, which provides both cost savings and potential VAT savings (EAG report consultation response form pg. 7). The first patient was administered SC natalizumab-TYS via THIS in [redacted], and new patient registrations, and overall patient numbers are [redacted] (Figure 1). The Company expects this [redacted] for the THIS program to continue based on the associated time and cost savings with [redacted] of unit SC sales under the program within 6 months, peaking at around [redacted].

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	Figure 1 New registrations and total patient numbers for the Tysabri Home Injection Service programme (as of February 2025)  The Company appreciates that Committee discussion explored the issue of continued availability of homecare-related services that are provided by manufacturers, and that ongoing patient monitoring may be more challenging in care settings outside of secondary care. Regarding ongoing provision of services, the Company wants to highlight its long-standing commitment to supporting these services in the UK across our MS portfolio (including for products with loss of exclusivity), and that the [redacted] should further alleviate these concerns. Regarding patient monitoring and safety, the Company would like to add that there are robust measures in place to monitor the risk of PML for patients enrolled onto THIS. Patients receiving treatment with natalizumab-TYS already possess a Patient Alert Card which contains important safety information that they need to be aware of before, during and after stopping treatment. In addition, the patients receive treatment by a healthcare professional (nurse) in their homes when they are enrolled onto THIS. The nurse goes through a comprehensive "outside of clinical setting" (OCS) checklist with the patient before each administration of natalizumab-TYS. This checklist has been reviewed and approved by the MHRA and is part of the risk management materials for natalizumab-TYS. It includes a decision tree for the healthcare professional to make a decision every time whether to administer treatment and involves close monitoring of any symptoms suggestive of PML. Similar robust measures will also be in place for [redacted] The Company firmly believes that any decision that does not take into account the benefits of the SC formulation of natalizumab-TYS is not reflecting the true value of the therapy.
2	Related to Comment 1, the Company does not believe that the following statement is factually accurate: ""The committee noted that subcutaneous administration of natalizumab was declining and clinical expert opinion is that home administration is rarely used in the NHS." The clinical experts at the meeting did not state this, instead they articulated that within their respective centres approximately 30-40% of natalizumab patients receive SC natalizumab-TYS, however due to a strict drugs committee within their centres, no further patients are allowed to switch from IV to SC administration. These experiences are not representative of all centres prescribing

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	natalizumab. Unit sale data for natalizumab-TYS indicates that SC natalizumab-TYS use is increasing, not declining, and it now represents ~[redacted]% of overall natalizumab-TYS unit sales.
3	The Final Guidance notes the uncertainty regarding natalizumab-TYS dosing in clinical practice, given the ability to use Extended Interval Dosing (EID). EID use in clinical practice has been confirmed by the Company with UK clinicians, both prior to dossier submission and after the Committee meeting. Company data shows that the average number of doses of natalizumab-TYS per patient per year is [redacted], not 13 as would be the case for Standard Interval Dosing [SID]). The Company agrees with the Committee's position that approximately 60% of patients receiving natalizumab in clinical practice would do so with an EID regimen. The Company believes that the evidence to date does not indicate any difference in efficacy or safety for natalizumab-TYS IV vs. SC, and the proportion of patients receiving both formulations via EID in the future is expected to be the same. Indeed, results from the natalizumab observational program presented at the European Academy of Neurology in 2024 show that efficacy was similar in patients switching from IV to SC formulation, regardless of SID or EID dosing (see CS section B.2.5.3.1, pg. 49). More generally, feedback from clinical experts to the Company suggests that EID is used routinely in clinical practice and that it also provides clinicians with the flexibility they need in deciding on appropriate therapy. Q6W dosing of SC natalizumab-TYS is particularly important for pregnant women and those with JCV-positivity, and feedback to the Company is that of the approximately 3 in every 4 patients receiving natalizumab who get SC Tysabri (vs the remaining 25% who receive IV natalizumab) at least two thirds are on 6-weekly dosing. Feedback to the Company from clinical experts is that EID is particularly valuable for patients who are pregnant, JCV-positive or have been on treatment for more than 2 years. Q8W dosing provides further dose frequency flexibility to support, for instance, maintaining outcomes during pregnancy. Overall, EID for natalizumab-TYS IV/SC (Q6W/Q8W) used in routine clinical practice in the UK and is associated with multiple benefits, namely: 1) cost savings due to reduced HCP time for administration; 2) reduction in natalizumab-TYS exposure during pregnancy; 3) reduction in risk of PML; 4) reduction in travel and in-clinic time for patients and carers (drug administrations). The Company believes that the Final Guidance should reflect the value that EID for natalizumab-TYS IV and SC provides to the NHS and patients.
4	The Company agrees with the Committee's preference for the EAG to explore EDSS-specific SMRs within the economic model, as reflected in our response to the EAG report and supported by clinical expert feedback from the first Committee meeting, relevant literature, and the Committee's preference in the recent appraisal of cladribine for treating relapsing multiple sclerosis (ID6263).[6–10] While acknowledging the limitations of Harding *et al*., as outlined in the NICE draft guidance for this appraisal, the Committee in the cladribine appraisal concluded that the SMRs in Harding *et al*. were the best available source of excess mortality in this population and aligned with the NHS population. Therefore, the Company considers that scenarios using EDSS-specific SMRs, at least partially informed by Harding *et al*., are more appropriate than the constant SMR from Jick *et al*. (2014),[11] which informed the EAG base case.
5	The Company is also concerned at the potential equality issues raised by the draft guidance. Natalizumab is the only high-efficacy therapy that clinicians in England and Wales are able to give

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	in pregnancy. Feedback from clinicians to the Company is that if a pregnant woman is not offered treatment, then this is a disadvantage and may lead to worse outcomes. For example, a case study in a pregnant woman where natalizumab-TYS was discontinued rapidly triggered a life-threatening case of immune reconstitution inflammatory syndrome (IRIS), which fully resolved on re-starting natalizumab-TYS later in pregnancy. The Company is therefore concerned at the potential for some patient groups, including pregnant women, to be disadvantaged by the current decision.
6	The Company would welcome further dialogue with NICE and the EAG on further updates to the economic model and analyses as access to key underlying data in the decision making inputs is currently limited e.g. MS registry. Areas for discussion would include, but not be limited to: • Additional information on the quality and relevance of the data from the MS Register, including completion of the DataSAT tool in NICE's real-world evidence framework for all potential data sources • The proportion of people with secondary-progressive MS in the model at 5, 10 and 15 years • Survival curves showing predicted survival in the model

References

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2. Edwards M. Evaluating the introduction of subcutaneous natalizumab to a cohortof patients with multiple sclerosis. Presented at the ABN Congress, 2022.

3. Biogen Data on File: DOF-0703. R-TYS-2024-GM-ENG-Budget Impact Model (BIM) Data for Tysabri Intravenous (IV) (v1.0). 2024.

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5. Mills R, Satkeviciute I, Davies H, Langdon D, Ando H, Young C. Natalizumab treatment satisfaction in the TONiC-MS study: latest results. P194. 2023 Presented at ABN;

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7. Harding K, Anderson V, Williams O, Willis M, Butterworth S, Tallantyre E, et al. A contemporary study of mortality in the multiple sclerosis population of south east Wales. Mult Scler Relat Disord. 2018 Oct;25:186–91.

8. Sadovnick AD, Ebers GC, Wilson RW, Paty DW. Life expectancy in patients attending multiple sclerosis clinics. Neurology. 1992 May;42(5):991–4.

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9. Pokorski RJ. Long-term survival experience of patients with multiple sclerosis. J Insur Med N Y N. 1997;29(2):101–6.

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Sandoz

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Name of commentator person completing form:	[redacted]

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1	While Sandoz were disappointed that the Committee were unable to recommend natalizumab at their first meeting, we recognise that this was due to the lack of appropriate analyses presented by the Assessment Group to align with the Committee preferences, and are hopeful that a second meeting will allow the Committee to recommend natalizumab within its licensed indication.
2	Sandoz welcome and agree with the following Committee conclusions in the draft guidance:

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	• Para 3.1 – that RRMS can have a substantial impact of quality of life • Para 3.2 – that natalizumab would be a welcome additional treatment option • Para 3.3 – that ocrelizumab (s.c. and i.v.), ofatumumab and ublituximab are relevant comparators (see below for our comments on cladribine); and that all other DMTs noted in the final NICE scope are not relevant comparators • Para 3.4 – that natalizumab improves disease control in people with highly active RRMS • Para 3.5 – that counselling and anti-JCV testing is a routine part of practice when using natalizumab • Para 3.9 – that the approach to comparative treatment effectiveness is acceptable for decision making • Para 3.12 – that it is appropriate to assume clinical equivalence between originator and biosimilar • Para 3.15 – that DMTs are stopped at EDSS 7 • Para 3.17 – that the EAG utility values are appropriate • Para 3.18 – that 60% of patients receiving natalizumab in the NHS receive extended interval dosing • Para 3.19 – that anti-JCV testing costs be excluded from the economic model • Para 3.20 – that it is appropriate to model equivalent resource use for s.c. and i.v. routes of administration
3	Sandoz agree in part with the following Committee conclusions but provide further comments to be considered at the second committee meeting: • Para 3.3 – that cladribine is a relevant comparator: Sandoz accept that cladribine is licensed, reimbursed and used to some degree in the NHS for the patient population covered by this appraisal, however Sandoz understand from commercially available market research data that cladribine use (in all positions) is low in the NHS and request that the Committee consider whether cladribine could for practical purposes be considered immaterial to the appraisal, which would therefore support Sandoz' proposal for a cost comparison of the high efficacy monoclonal antibody DMTs. Sandoz would note that analysis from the global MSBase cohort have demonstrated that cladribine is less effective than the most potent intravenous MS therapies, including natalizumab (Roos et al 2024. Available to download free-of-charge https://journals.sagepub.com/doi/10.1177/13524585241267211). Sandoz would also note that, unlike natalizumab, cladribine is contraindicated in pregnancy and breast feeding. • Para 3.6 – that the EAG's NMA is appropriate for decision making; Sandoz considers this a practical conclusion in the context of the conclusion on comparators in para 3.3 but notes that the EAG's NMA was open to criticism, as we have previously commented on. • Para 3.7 – that a cost comparison of ocrelizumab, ofatumumab and natalizumab could be informative but that ublituximab and cladribine were also relevant; having initially proposed the cost comparison approach, Sandoz would suggest further expanding it to include

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	ublituximab alongside ocrelizumab and ofatumumab and, as noted above, Sandoz request that the Committee reconsider how material cladribine is for this appraisal. Such an analysis would logically extend the approach taken by the Committee in TA1025 where ublituximab was recommended on the basis of cost comparison with ofatumumab and ocrelizumab. • Para 3.8 – that the EAG's DES model is appropriate for decision making; Sandoz consider the EAG's DES model to be overly complex, lacking in transparency and to be so computationally inefficient to run that it forms a barrier to effective participation by consultees, nonetheless Sandoz are willing to proceed with participation in the appraisal given the many positive Committee conclusions welcomed above. As noted elsewhere in this response, Sandoz continue to consider that a cost comparison approach versus the relevant high efficacy monoclonal antibody DMTs identified by the Committee would be the most practical economic analysis. • Para 3.10 – the Committee identified the source of natural history data as being a source of uncertainty in the appraisal; Sandoz reiterate that a cost comparison approach, as justified above, would avoid this source of uncertainty and thus be preferable for decision making, given the committee's many positive conclusions welcomed above. • Para 3.11 – similar to our comment on para 3.10, Sandoz reiterate that a cost comparison approach, as justified above, would avoid this source of uncertainty and thus be preferable for decision making, given the committee's many positive conclusions welcomed above. • Para 3.13 – similar to our comment on para 3.10, and 3.11, Sandoz reiterate that a cost comparison approach, as justified above, would avoid this source of uncertainty and thus be preferable for decision making, given the committee's many positive conclusions welcomed above. • Para 3.14 – similar to our comment on para 3.10, 3.11 and 3.13, Sandoz reiterate that a cost comparison approach, as justified above, would avoid this source of uncertainty and thus be preferable for decision making, given the committee's many positive conclusions welcomed above. • Para 3.15 – similar to our comment on para 3.10, 3.11, 3.13 and 3.14, Sandoz reiterate that a cost comparison approach, as justified above, would avoid this source of uncertainty and thus be preferable for decision making, given the committee's many positive conclusions welcomed above.
4	In response to the Committee's requests for additional input and analysis from the Companies in Para 3.23 for "Any relevant information regarding clinical equivalence of originator and biosimilar": • Guidance on the licensing of biosimilar products - GOV.UK: "Once authorised, a biosimilar product is considered to be interchangeable with their RMP, which means a prescriber can choose the biosimilar medicine over the RMP (or vice versa) and expect to achieve the same therapeutic effect. Likewise, a biosimilar product is considered to be interchangeable with another biosimilar to the same RMP. As a result of interchangeability, switching patients from one product to another (RMP or biosimilar) has become clinical practice. The decision rests with the prescriber in consultation with the patient, in line with the principles of shared decision making; both need to be aware of the brand name of the product received. " • NICE position statement on biosimilars in appraisals: "Recommendations will refer to the British approved name of the medicine and will not differentiate between the originator and

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	biosimilar products. The guidance will state that treatment should be initiated with the cheapest available product. In acknowledgment of the fact that the EMA does not make recommendations on whether a biosimilar should be used interchangeably with its reference medicine, or with other biosimilar medicines, the issue of switching and interchangeability will not be considered within the technology appraisal."
5	In response to the Committee's requests for additional input and analysis from the Companies in Para 3.23 "A scenario assuming clinical equivalence for natalizumab, ocrelizumab and ofatumumab" • Sandoz have updated their cost comparison analysis from their original evidence submission to align with the committee preference on: o adding ublituximab as a comparator o considering s.c. ocrelizumab in addition to i.v. o assuming 60% of patients receive natalizumab extended interval dosing o to assume equal resource use for s.c. and i.v. for DMTs administered in hospitals, namely a Day Case cost for AA30F from the NHS Cost Collection o to update the cost used for hospital administration to the latest published NHS Cost Collection for 2023/24, which was published after the original Sandoz evidence submission • The results of this analysis, undertaken over a three-year time horizon, show that natalizumab biosimilar has the lowest modelled cost for all comparators at list price. • Given the need for NICE to undertake analyses at the confidential NHS prices of all DMTs, Sandoz has provided a working CMM model in Excel with built-in functionality for NICE to undertake these analyses themselves using the Sandoz model. • Sandoz request that results incorporating confidential NHS prices produced by NICE from the Sandoz CMM are presented to the Committee at the Committee meeting independently of any EAG analyses.
6	In response to the Committee's requests for additional input and analysis from the Companies in Para 3.23 "Exploring alternative ways to model treatment waning": • A clinical expert consulted by Sandoz during the DG consultation was of the opinion that the treatment effect of a DMT is binary, either it works or does not work and discussing treatment waning in MS is not helpful. • Sandoz are concerned that conceptual arguments on waning of treatment effect are inherently uncertain and not amenable to evidence; in the context of the cost of natalizumab reducing to biosimilar pricing levels following loss of exclusivity, Sandoz request that Committee consider the decision problem at hand pragmatically.
7	In response to the Committee's requests for additional input and analysis from the Companies in Para 3.23 "Data on subsequent treatments in NHS clinical practice": • Sandoz firstly note that the Committee request for evidence on the split of subsequent treatments between ublituximab, ocrelizumab and ofatumumab cannot be answered with evidence from NHS practice, given that ublituximab was only recommended by NICE on 18th December 2024, with a 30-day implementation period ending on 17th January 2024.

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	As such, there have only been two months of availability on the NHS which is insufficient time to reach a new equilibrium in prescribing practice. • Sandoz suggest that this is pragmatically addressed with a set of scenario analyses assuming 100% usage of each of ublituximab, ocrelizumab and ofatumumab to determine whether this uncertainty is of material relevance to any ICER produced by the EAG model.
8	In response to the Committee's requests for additional input and analysis from the Companies in Para 3.23 "Exploring alternative ways to model mortality": • A clinical expert consulted by Sandoz during the DG consultation was of the opinion that the Harding data (Harding et al 2018) gives unrealistic increases in mortality rate with increased EDSS scores. Other data sets suggest the risk goes up 2–3 times which is much more realistic. • As such, Sandoz consider that the Committee should adopt a pragmatic approach to this issue and consider calibrating between sources to derive SMRs that do increase with EDSS but where that increase is more realistic than the Harding data
9	In response to the Committee's requests for additional input and analysis from the Companies in Para 3.23 "Data on the proportion of people having 6-weekly dosing in NHS clinical practice": • Sandoz welcome the Committee's conclusion on 60% usage of extended interval dosing • A clinical expert consulted by Sandoz during the DG consultation was of the opinion that EID was expected to become more and more common over time to control PML risk

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about funding from the company and links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into one response. We cannot accept more than one set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- In line with the NICE Health Technology Evaluation Manual (sections 5.4.4 to 5.4.21), if a comment contains confidential information, it is the responsibility of the responder to provide two versions, one complete and one with the confidential information removed (to be published on NICE's website), together with a checklist of the confidential information. Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please submit a second version of your comments form with that information replaced with asterixis and highlighted in black.
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- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments

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without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.

- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	MS Society with input from the patient expert nominated

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

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Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	We are disappointed by the initial decision not to recommend natalizumab and its biosimilar for use in people with highly active relapsing remitting MS (RRMS) despite a full course of another disease modifying therapy (DMT). Recommending natalizumab for this group would increase patient choice for people with highly active RRMS. People in this group are already offered natalizumab in Wales, Scotland and Northern Ireland, so a recommendation would reduce geographical disparity in access to a high efficacy DMT in the UK. People with MS often face profound uncertainty(1), and we know that choosing a DMT is a highly personal decision requiring each individual to consider the risks and benefits – for them – of the different DMTs(2). The more effective treatments are available to wider populations, the greater the choice for patients. (1) Van Reenen et al. (2025) The liminal space between hope and grief: The phenomenon of uncertainty as experienced by people living with relapsing-remitting multiple sclerosis Available at: https://pmc.ncbi.nlm.nih.gov/articles/PMC11774396/ (2) Manzano, A. et al. (2019) CRIMSON - Considering Risk and benefits In Multiple Sclerosis treatment selection: Final Report
2	A decision not to recommend natalizumab may have a disproportionate impact on people of childbearing age, and particularly women, who are more likely to consider family planning and pregnancy in their treatment decisions. Pregnancy and maternity are protected characteristics. There is no evidence that natalizumab harms unborn children, and treatment is generally continued through pregnancy. Of the comparator DMTs for this appraisal, courses of ocrelizumab (subcutaneous and intravenous), ofatumumab and ublituximab are paused during pregnancy. Cladribine is the only comparator that someone can benefit from for the full duration of pregnancy, though restrictions remain as pregnancy should be delayed until 6 months after the year 2 dosage. Unlike natalizumab, cladribine is classified as having ‘good efficacy’.

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	This means that a decision to recommend natalizumab would make it the only high efficacy DMT available to this population without restrictions on family planning. This would address a currently unmet need and potential gendered inequality to high efficacy DMTs, reported elsewhere(1). As our patient expert puts it, 'empowering people living with MS to effectively treat their MS whilst also providing opportunities for them to fulfil other ambitions is critical. For women with MS who would like to grow their families and are planning pregnancies, there are very few choices for them to fulfil both these ambitions. Reflecting on my own experience as a young woman whose MS was highly active being faced with the potential choice of prioritising a more effective treatment or having a baby, it made a significant difference talking to my neurologist and the specialist pregnancy nurse who informed me that I didn't have to choose one or the other with the option of natalizumab. Managing physical and mental health is an important part of living well with MS and something I don't think should be underestimated.' (3) Vukusic, S., et al. (2024). Is there therapeutic inertia in women with MS? Presented at ECTRIMS 2024
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Insert extra rows as needed

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Multiple Sclerosis Trust

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InPlease disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

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1	We think that some commentators may be underestimating the prevalence of Advanced MS. Many people living with advanced and complex symptoms of MS will not be under the care of Neurology teams but will be cared for directly by General Practice and District Nursing, or alternatively in Palliative Care or residential care homes. Our research indicates that there could be as many as 40,000 people with Advanced MS in the UK, although this is hard to determine as they may not appear on Neurology caseloads and there are issues with coding patients in GP records. This means that the chances of a person with RRMS proceeding to advanced states of disability may be higher than the model suggests. The costs to the NHS of caring for people in advanced stages of MS, including hospital admissions for things like UTIs and falls needs to be considered.
2	We hear from people taking natalizumab and from health professionals (including at our annual Conference earlier in March 2025) that extended interval dosing is very common and widely accepted. This means that the real-world costs of natalizumab are less than indicated. This is also particularly relevant in the context of treating women with MS through conception, pregnancy and post-childbirth. There is a high chance of post-birth rebound activity in women with highly active MS, meaning that they are at risk of relapse if they stop controlling their MS during pregnancy. By utilising the extended interval dosing, they can time their infusions to avoid the third trimester, (which is the only point at which natalizumab may influence the baby) and restart in time to resume maternal protection.
3	The recommendations as they stand represent a disappointing outcome for women with highly active MS planning pregnancy and this is **a significant equalities issue**. These women will now face devastating choices – to expose their foetus to a drug with known negative side-effects (all the relevant comparators), to not take any disease modifying drug and expose themselves to the risk of catastrophic and permanent disability at the point of becoming a mother to a newborn, or to not become a mother at all. This is very serious, and we feel strongly that natalizumab should be considered as an option for neurologists supporting women of childbearing potential with highly active RRMS. As women are up to three times more likely to get RRMS than men, this is a significant problem and will lead to harm for women and families.
4	To people living with RRMS, the distinction into different forms or types is meaningless. These categorisations are somewhat recursive, based in part upon assessing how effective a previous treatment has been. If you've been lucky enough to select a drug that works first time, you might think your MS was relatively inactive, when it was simply a good match between your treatment and your personal physiology. Until we know why some people respond better to some disease modifying drugs than others, it makes no sense to restrict the ability of neurologists and patients to make a choice where lifestyle and other considerations With AI support of DMD prescription choices being developed (e.g. Personalised Treatments Group, Cambridge) coming in due course, not having this flexibility could further delay prescription accuracy, subject people to unwarranted side effects and less effective treatments, and cause higher spending than needed by the NHS.
5	We know there are situations where natalizumab is being given at home by a health professional, to the benefit of patients who are otherwise unable to travel. We think it is important to consider this option, as there are many reasons why patients with MS might be unable or unwilling to travel long distances, including comorbidities (very common in MS), disabling symptoms, and cost. We

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	know patients who have chosen therapies based on the travel required, making this an equalities issue based on household income.
6	

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Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	We read with disappointment the draft TA finding that natalizumab would not be recommended for use in the NHS in those with highly active MS.

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	We feel that this recommendation does not take into account the substantial clinical value that being able to use natalizumab according to the current license would bring. There is a need for a non-immunosuppressive treatment option for people with MS failing first line treatment. Natalizumab is the only highly effective therapy for MS not associated with systemic immunosuppression. During the COVID-19 pandemic, natalizumab was temporarily available for people with highly active MS due to its mechanism of action (in contrast to other therapies associated with higher risk of severe COVID); this was highly valued by both patients and clinicians. Additionally, natalizumab can be started more rapidly than other highly effective treatments, without the need for prescreening and potential vaccination (varicella, mumps, pneumococcus etc). This is a hugely desirable quality where a treatment switch is needed urgently due to clinical deterioration. These recommendations are in contrast with clinical practice in other European countries, placing patients treated in England at significant disadvantage.
2	We note that the cost analysis of natalizumab presented in the draft TA refers to 4-weekly dosing. Many centres are now using 6-weekly dosing for the majority of patients as part of PML risk mitigation and management of infusion suite capacity. With reduced treatment frequency, both drug and NHS infusion-associated costs reduce by c33%, in addition to potential reduction in costs associated with safety monitoring given risk mitigation. Subcutaneous administration, whilst predominantly given in hospital, saves staff hours through shorter administration times, whilst continuing to deliver this treatment in safe environment.
3	We additionally raise the following equalities scenarios which we believe have not been fully taken into account: Natalizumab treatment is safe during pregnancy, and its continuation is recommended during conception and pregnancy according to both UK and international guidance. Where patients on antiCD20s have breakthrough inflammatory disease, they currently have no pregnancy-compatible DMT to escalate to without waiting for a second clinical relapse. Men in this situation have the option of fingolimod (teratogenic) or alemtuzumab/cladribine (induction therapies with long washout). Women wishing to try to conceive should not take these therapies whilst trying to conceive. Lack of access based on not meeting the relapse criteria mean that

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	women who are pregnant or trying to conceive are excluded from having access to appropriate treatment. A PPP based on this consideration was being prioritised for consideration by NHSE on an equalities basis prior to this MTA; this was suspended as a result of this MTA. Secondly, in older patients with MS where the risk of infections is particularly increased, natalizumab may offer a safer non immunosuppressive treatment option in the context of active disease.
4	References 1. NHS England DMT algorithm https://www.england.nhs.uk/wp-content/uploads/2024/03/treatment-algorithm-for-multiple-sclerosis-disease-modifying-therapies-july-23.pdf 2. Smets et al 2022. https://pubmed.ncbi.nlm.nih.gov/34902761/ 3. Giovannoni et al 2021 https://pmc.ncbi.nlm.nih.gov/articles/PMC8286545/ 4. Dobson et al 2019. https://pubmed.ncbi.nlm.nih.gov/30612100/ 5. Fillipi et al 2024. https://pubmed.ncbi.nlm.nih.gov/37715789/
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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Wallace Brownlee

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Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	Wallace Brownlee

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	I was disappointed to learn of the Committee's decsion. I am concerned that the benefits of having this option to patients with MS, including those with protected characteristics have not been taken into account. Situations where natalizumab maybe partiuclartly helpful include women who are pregnant, breastfeeding, or actively trying to concieve; older patients who are at risk of infectious complications from other approved therapies; and people with certain comorbidities that complicate management decisions.

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2	I'm concerned that the decision taken has been driven by incorrect modelling which is not reflective of current UK practice. For example, extended interval dosing of natalizumab is now regularly used in many centres with the drug given 6 weekly rather than 4 weekly. This was not well accounted for in the model evaluated.
3	The Committee cited a source of uncertainty as the clinical equivalence of natalizumab originator and biosimilar. Biosimilar natalizumab has been approved by the MHRA who have a have regulatory responsibility for determining equivalence of a biosimilar, and following approval the medicines are considered to be equivalent and this is how they are already being used in the NHS. It is unclear what the basis is for the Committee's uncertainty.
4	The Committee mentions concerns regarding how best to model natural history of MS, treatment waning and mortality. These are issues that other Committees have raised previously and are generic rather than specific to this drug. It is disappointing that there has not be learning from previous (successful) appraisals for MS therapies that could have been applied here.
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	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced.
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	

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NICE National Institute for Health and Care Excellence

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

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 02 April 2025. Please submit via NICE Docs.

Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	**My institution has previously received research funding from Biogen for research led by myself (2021-2022).** **My institution currently receives research funding from Imperial College for a project funded by Biogen (2018-present).** **My institution has received compensation for my time from Sandoz (2023-2024) and Biogen (2022).** **My institution has previously received research funding from Merck for research led by myself (2021-2022).** **My institution currently receives research funding from Imperial College for a project funded by Merck (2018-present), previously additionally funded by Celgene (2019-2021).** **My institution has received compensation for my time from Janssen (2020-2022), Novartis (2022), Roche (2022-2024), and Merck (2019).** **I am currently a PI on a clinical trial sponsored by Roche (2021-present) for which my institution receives support.**
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	Ruth Dobson

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	I was disappointed to read the negative TA, which was essentially based on a lack of direct comparative and cost data leading to challenges with the modelling. This decision leaves people with MS who have disease activity on highly effective first line therapy (antiCD20 or cladribine) without access to a highly effective treatment unless they wait for a second relapse. The result of this decision will be irreversible disability for some people living with MS. I note that the committee concluded that natalizumab would be a welcome additional treatment option for people with highly active RRMS, but did not find it suitable on the basis of complex

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	statistical models rather than the clinical and patient need. Natalizumab has a unique mechanism of action which is not immunosuppressive. For people who have breakthrough relapse following cladribine, this negative TA means that their only options are long term immunosuppression or HSCT. The ability to use natalizumab after a single breakthrough relapse would offer patients who have developed disease activity after such treatments a non-immunosuppressive option. To my mind, as a clinician, this is a decision based on the absence of ability of statistical models to capture real world complexity and patient need. The recent TA recommending the availability of cladribine for people with active MS requiring high efficacy treatment leaves natalizumab as the only product requiring 2 relapses on treatment for escalation. There is an equalities issue here for those who relapse on antiCD20 therapies; as pregnancy is contraindicated within 6 months of taking cladribine treatment, those who relapse on antiCD20 therapies and wish to get pregnant within 18 months will have no available effective treatment with a safety record in pregnancy to use. Given that cladribine has similar wash out periods for males and females, and that the population seeking more rapid pregnancy are likely to be older this decision discriminates on the basis of age and pregnancy.
2	
3	
4	
5	
6	

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about funding from the company and links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into one response. We cannot accept more than one set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- In line with the NICE Health Technology Evaluation Manual (sections 5.4.4 to 5.4.21), if a comment contains confidential information, it is the responsibility of the responder to provide two versions, one complete and one with the confidential information removed (to be published on NICE's website), together with a checklist of the confidential information. Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please submit a second version of your comments form with that information replaced with asterixis and highlighted in black.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments

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NICE National Institute for Health and Care Excellence

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

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 02 April 2025. Please submit via NICE Docs.

without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.

- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, 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 our consultations 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.

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Multiple Technology Appraisal

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

Comments on the draft guidance received through the NICE website

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	UK Multiple Sclerosis Specialist Nurse Association (UKMSSNA)
Location	Not specified
Conflict	None
Notes	None

Comments on the DG:

- Has all of the relevant evidence been taken into account?

Is it possible to use data from blueteq to compare the current cost of Natalizumab for this indication?

- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Cost effectiveness appears comparable to Ocrelizumab and Ofatumumab and emphasis should be placed on its utility around pregnancy and family planning for patients with highly active disease.

- Are the recommendations sound and a suitable basis for guidance to the NHS?

Based on the evidence provided, Natalizumab is an effective treatment and provides a useful option for patients with highly active disease. There does not seem to be any evidence provided to suggest Natalizumab is not cost effective in comparison to Ocrelizumab and Ofatumumab.

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

I do not think the recommendations would be classified as unlawful discrimination but as previously stated, reducing access to this disease

modifying therapy may negatively impact people who are actively trying to become pregnant.

- Draft guideline, section 1.2, ‘Because of the uncertainties in the economic model, it is not possible to determine the most likely cost-effectiveness estimates for natalizumab.’

Not taking into account the common use of extended interval dosing, the cost of Natalizumab per year seems comparable to Ocrelizumab and Ofatumumab based on the pricing available through BNF (and not taking into account NHS discount)

- Draft guideline, committee-discussion, Equality, section 3.25,’ The committee recalled that natalizumab had proven safety data in pregnancy, so a positive recommendation for natalizumab in highly active RRMS would address this unmet need.’

I would like to emphasize this point as something that sets Natalizumab apart from Ocrelizumab and Ofatumumab. Many people with MS are diagnosed at a time when they are planning a family and having a highly effective disease modifying therapy that can be used throughout pregnancy will reduce the risk of relapse and increased disability in young mothers.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	University Hospitals Birmingham NHS Foundation Trust
Location	Not specified
Conflict	None
Notes	None

Comments on the DG:

- Draft guideline

NO acknowledgement for time of infusions and consumsables that are used

- Draft guideline, section 1.2

As knowledge regarding MS and relapses have expanded. It is regarded that treating MS aggressive will/may slow brain atrophy. This essential in long term management of MS and consequently ensuring people with MS can stay at work and they may access Health care re Hospital/GP services thus sagving money and resources

- Draft guidance, information-about-natalizumab, Marketing authorisation indication, section 2.1

These statement are no consisitent with other High efficay treatments. re CD 19 drugs have potential for long term Cd 20 suppression

- Draft guidance, information-about-natalizumab, Price, 2.4

for S/C- comes in prefilled syringes so no consumables are required. in hosptial less time, so more patients can be treated than IV tyruko and IV OCrevus. therefore less wait time for treatment

- Draft guidance, information-about-natalizumab, Price, 2.5

this is the cost price - IV Tyruko- longer stay in hospital 1hour, need cannula, saline flush, giving set and pump. no cost in the document for the consumable that are need by the trust administering the IV. there are hidden costs that have not been taken into consideration

- Draft guidance, committee-discussion, Details of condition, section 3.1, ‘he patient expert explained that many people feel a loss of independence when diagnosed with an incurable condition such as MS. As the condition progresses, people become increasingly disabled, which can worsen their quality of life and that of their carers. The committee concluded that RRMS can have a substantial impact on quality of life.’

therefore treating patients earlier will benefit the above and keep people at work and less time of work

- Draft guidance, committee-discussion, Details of condition,Treatment waning, section 3.13

need more real world data.

- Draft guidance, committee-discussion, Subsequent treatments in the model, section 3.14, ‘The EAG highlighted that 35% of people in the model had third-line treatment (that is, 1 additional subsequent treatment) and 34% of people had fourth-line treatment (a second subsequent treatment) over the modelled lifetime.’

it treat adequatly at first will prevent swapping DMTs and this wastage that occurs

- Draft guidance, committee-discussion, Subsequent treatments in the model, section 3.14, ‘People who developed secondary-progressive MS were assumed to have a basket of siponimod or interferon beta 1b as a weighted average by use in the MS Register’

not all patients can recieve Siponimod re criteria, genotype testing and contraindications

- Draft guidance, committee-discussion, Natalizumab dosing regimen, section 3.17

no consumables have been acknowledged in the costing and more time taken infuison chair

- Draft guidance, committee-discussion, Natalizumab administration routes, section 3.20, ‘he company that makes natalizumab originator said that subcutaneous natalizumab was associated with reduced administration time and so reduced treatment burden and NHS costs. T’

we see this in practice

- Draft guidance, committee-discussion, Equality, section 3.25

this can be used in pregancy and it is acknowledge post partum there may be a risk of more relapses and can breast feed on Tysabri.

Bristol TAG commentary on consultation documents

1 Commentary on the consultation comments from companies and other stakeholders

Consultation comments were received from the two companies (Sandoz and Biogen) and from five additional stakeholders: Association of British Neurologists (ABN), the MS Society, the MS Trust, Dr Dobson and Dr Letissier. Appendix 1 provides an overview of each comment received on the EAG report and draft guidance together with a summary of the EAG response.

Key issues highlighted by the consultation include:

1.1 Consideration of cost-comparison approach

Sandoz reiterated their reasoning for requesting that this appraisal should be a cost-comparison rather than an MTA with comparison with ocrelizumab and ofatumumab.

EAG response:

As NICE highlighted in response to consultation comments on the scope "NICE's position statement on biosimilar technologies 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."

The EAG provide a critique of the cost-comparison submitted by Sandoz below and have re-run the cost-comparison using confidential discount prices (confidential Appendix).

The company submission compared the total of acquisition and administration costs of natalizumab originator and natalizumab biosimilar against ocrelizumab, ublituximab and ofatumumab but not cladribine over a 3 year time horizon. Extended Interval Dosing (EID) at 100% or at 60% for both originator and biosimilar were included as options. If not using EID, ofatumumab was found to have lowest costs (£54,583). If using 100% EID natalizumab biosimilar was found to have lowest costs (£43,547) and if using 60% EID natalizumab biosimilar was also found to have lowest costs (£48,413).

The model was limited by only using a 3 year time horizon, 3.5% discount rate, not modelling natural history, mortality, not applying any discontinuation, and not considering treatment

switching. The latter two could influence results regardless of the assumption of equal efficacy as costs vary across treatments. The equal efficacy assumptions equalise costs accrued through events, as relapses and EDSS progression are assumed equivalent. Progression to SPMS, with its higher treatment and care costs, was also not considered.

The costs are largely in line with EAG assumptions with some notable differences. The Annual treatment costs are equivalent to EAGs with the exception of Ublituximab where we assume a higher number of doses as detailed in section 2.2 and Natalizumab EID as detailed in section 1.7. The Administration costs are lower £513 in comparison to £626.13 per visit assumed by EAG but the number of visits are equivalent. Treatment monitoring costs were not included but necessary for because EAG was advised that patients are routinely monitored in tertiary care for disease activity and treatment side effects.

1.2 Choice of comparators

Sandoz restated their concern raised in the consultation on the scope that Cladribine should not be considered as a comparator as use in the NHS is low.

EAG response:

The EAG included cladribine in the appraisal following the scope specified by NICE. As NICE highlighted in response to consultation comments on 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." Cladribine was furthermore included in the analyses requested by the committee following meeting 1.

1.3 Safety of natalizumab in pregnant and breast-feeding women and older patients

All those that provided comments on the report highlighted that the safety of natalizumab in pregnant and breastfeeding women should be considered an equality issue as natalizumab may be the only appropriate treatment option for this group.

Some also raised that in older patients with MS where the risk of infections is particularly increased, natalizumab may offer a safer non immunosuppressive treatment option in the context of active disease.

EAG response:

The EAG agrees that this is an important equality issue and should be considered as part of the decision making process.

1.4 Complexity of EAG model

Sandoz consider the EAG's DES model to be overly complex, lacking in transparency and to be computationally inefficient to run

EAG response:

To overcome the key criticisms of the previous manufacturer models for RRMS submitted to NICE the EAG adopted an individual-level discrete-event simulation (DES) model. This makes it possible to model treatment sequences and, if desired, enable treatment-specific waning patterns. The inflexibility of cohort Markov models made it difficult to accurately reflect the course of MS, leading to implausible numbers of patients in the high EDSS states. The flexibility

of DES better reflects the natural course of MS, and eases the inclusion of new standardised mortality rates by EDSS.

Regarding efficiency, the EAG used 1000 samples and 1000 patients through a high performance computing (HPC) facility, which did take time to run. However, as noted in the original EAG report, the model results converge with only 100 samples and 100 patients. This scope of simulation can be run in under an hour on desktop or laptop computers and is robust for decision making.

On transparency, all model R code and data have been provided, including documentation and data lists as requested by NICE and stakeholders. The code itself is fully commented and uses open-source R packages and the open-source R software, rather than hidden Visual Basic functions in the close-source Excel software. Unlike previous RRMS models submitted by manufactures to NICE, the EAG R model will be released publicly on GitHub for free use by the community.

1.5 Treatment waning

Sandoz highlight that a clinical expert that they consulted was of the opinion that the treatment effect of a DMT is binary, either it works or does not work and discussing treatment waning in MS is not helpful.

EAG response:

The EAG clinical advisers indicated that waning is not the correct concept in DMTs for HARRMS. Instead, the discussion is around 'breakthrough' disease for RRMS and this is detected either radiologically whenever a scan happens to be done and/or clinically as relapses. Although there may be disease in the background, treatment 'failure' is only detected at discrete time points. The advisers would generally allow for 6 months on therapy before defining treatment failure, at least for B cell therapies.

The advisers noted anecdotally that most people destined to fail seem most likely to do so in first 2 years. However, a recent audit by one of the advisers objectively showed that breakthrough activity on routine surveillance MRIs are at a fairly stable rate of ~5-10% up to 5 years on DMTs. The EAG ran a treatment waning scenario informed by this advice where the annal rate of waning is 2% for the first 5 years on treatment (i.e., a total of 10% waning) and that rates of relapse and EDSS increase increase by this amount each year across all treatments.

Results are provided in Section 5.2.

1.6 Subsequent treatments

Sandoz noted that the Committee request for evidence on the split of subsequent treatments between ublituximab, ocrelizumab and ofatumumab cannot be answered with evidence from NHS practice, given that ublituximab was only recommended by NICE on 18th December 2024, with a 30-day implementation period ending on 17th January 2024. They suggested that the EAG should address this pragmatically with a set of scenario analyses assuming 100% usage of each of ublituximab, ocrelizumab and ofatumumab to determine whether this uncertainty is of material relevance to any ICER produced by the EAG model.

EAG response:

In response to this request, the EAG have conducted scenarios assuming 100% of patients switch to ocrelizumab, ofatumumab and ublituximab as subsequent treatment. There is no efficacy or safety evidence on ublituximab so it is assumed equivalent to ocrelizumab. Results are provided in Section 5.2.

The EAG base case has also been modified to use data on subsequent treatments from the MS Registry, which is provided in Table 1.

TABLE 1 PROPORTION OF PATIENTS ON 2ND LINE & 3RD LINE TREATMENTS MS REGISTRY ANALYSIS

	HARRMS		All other RRMS	
Treatment	**n**	**%**	**n**	**%**
2nd line therapies				
Natalizumab	17	19%	8	24%
Cladribine	17	19%	4	12%
Ocrelizumab	34	37%	16	47%
Ofatumumab	23	25%	6	18%
Total in Scope	91		34	
Other therapies out of scope	156		79	
3rd line therapies				
Natalizumab	2	8%	2	15%
Cladribine	5	19%	1	8%
Ocrelizumab	9	35%	7	54%
Ofatumumab	4	15%	2	15%
Total in Scope	20		12	
Other therapies out of scope	26		13	

1.7 Extended interval dosing

Several of the comments highlighted the extended interval dosing (EID) is currently in use in the NHS, supporting the Committee's conclusion on 60% usage of extended interval dosing. Sandoz highlighted that a clinical expert that they consulted during the DG consultation was of the opinion that EID was expected to become more and more common over time to control PML risk. Biogen commented that company data shows that the average number of doses of natalizumab-TYS per patient per year is [redacted], not 13 as would be the case for Standard Interval Dosing [SID]). The ABN also highlighted that many centres are now using 6-weekly dosing for the majority of patients as part of PML risk mitigation and management of infusion suite capacity. With reduced treatment frequency, both drug and NHS infusion-associated costs reduce by c33%, in addition to potential reduction in costs associated with safety monitoring given risk mitigation.

EAG response:

The EAGs clinical advisers indicated 50% usage in one centre and 0% in another as keeping to the licensed dose as per Blueteq requirement for NHS England. The EAG therefore keep the

base case at the committee's requested level of 60% usage and EID is [redacted] which now aligns with the proportion indicated by Biogen's calculations.

1.8 Potential workload savings and reduction in NHS and patient burden associated with the SC formulation of natalizumab (Biogen and Dr Latissier)

Biogen highlighted potential cost savings to the NHS of the SC formulation of natalizumab when administered in a secondary care setting in terms of: reduction in staff hours through shorter administration times, infusion chair time, and equipment costs. Increased infusion suite capacity also allows more MS patients to be treated reducing waiting lists. Dr Latissier also raised these potential advantages noting that SC natalizumab comes in prefilled syringes so no consumables are required and that less time in hospital is required so more patients can be treated than with IV tyruko and IV OCrevus. In contrast, IV Tyruko requires a longer stay in hospital 1hour, needs a cannula, saline flush, giving set and pump. The economic model did not appear to take these costs into account.

EAG response:

The EAG's clinical advisers note that the potential cost savings highlighted by the company are plausible. Biogen estimates a total cost savings [redacted] per year assuming all patients (n=500) are treated with the SC formulation. Drawing on [redacted] savings in administration and observation nursing time per year, [redacted] increase in nursing capacity (number of patients serviced per nurse) and [redacted] savings in IV consumables.

The EAG appreciate that while Biogen's costing is detailed and informative, it does not align with appraisals of MS as they do not cost with the HRG4+ grouper cost per patient visit. The EAG model does not model staff hours (patient in chair time and pharmacy nursing staff time) but does model some time savings in scenario 1. The EAG have assumed a 50% reduction in administration / observation day case cost of £626.13 but not on monitoring visits, as clinicians indicated that monitoring time would be the same regardless of formulations. Taking Biogen's approach the Day case cost for (n=500) patients is £313,065 and a 50% reduction factor used in scenario 5 amount to an annual saving of £156,532.

The EAG note that the [redacted]

1.9 Use of EDSS specific SMRs (Biogen)

Biogen noted that they supported the Committee's preference for the EAG to explore EDSS-specific SMRs within the economic model. They proposed that scenarios using EDSS-specific SMRs, at least partially informed by Harding *et al.*, are more appropriate than the constant SMR from Jick *et al.* (2014), which informed the EAG base case.

EAG response:

The EAG have followed the feedback to explored EDSS-specific SMRs informed by both Harding 2018 and Jick 2014.(3, 4) These are described in Section 2.1 and used in both the committee and updated EAG base case.

1.10 Specific issues with the model (Biogen)

The Company would welcome further dialogue with NICE and the EAG on further updates to the economic model and analyses as access to key underlying data in the decision making inputs is currently limited e.g. MS registry. Areas for discussion would include, but not be limited to:

- Additional information on the quality and relevance of the data from the MS Register, including completion of the DataSAT tool in NICE's real-world evidence framework for all potential data sources
- The proportion of people with secondary-progressive MS in the model at 5, 10 and 15 years
- Survival curves showing predicted survival in the model

EAG response:

In collaboration with the MS Registry, the EAG have completed the requested DataSAT tool and provided it in the Appendix.

The EAG have also calculated the proportion of people with secondary-progressive MS in the model at 5, 10 and 15 years, and provided survival curves in Section 5.3.

1.11 Starting on natalizumab treatment (ABN)

The ABN highlight that natalizumab can be started more rapidly than other highly effective treatments, without the need for prescreening and potential vaccination (varicella, mumps, pneumococcus etc). This is a hugely desirable quality where a treatment switch is needed urgently due to clinical deterioration.

EAG Response:

The EAG clinical advisers note that this issue is not straightforward, as delays can occur at multiple stages of the treatment pathway and are often specific to individual centres, depending on local challenges or bottlenecks. For example, in some centres there may be delays in accessing an infusion bed—delays that can rival those associated with vaccination. As a result, treatments that do not require an infusion bed, such as cladribine, ofatumumab, or SC natalizumab, may be initiated more quickly.

The advisers also emphasise that the need for new vaccinations prior to starting a DMT is relatively uncommon—typically only necessary if a patient is found to be varicella-negative. While delays can occasionally arise from TB screening prior to initiating B-cell therapies, this is also reported to be rare. In the case of natalizumab, delays can sometimes be caused by JC virus testing, and clinicians also note that patients often need time to fully understand and come to terms with the risks associated with PML.

2 Additional analyses

In response to the consultation comments and requests from the committee we have conducted the following additional analyses:

2.1 Mortality calculation

The previous EAG model used standardised mortality ratio (SMR) from Jick 2014 based on data from the UK General Practice Research Database.(4) This study compared all-cause mortality in a cohort of MS patients (N=1,822), diagnosed between 1993 and 2006, against a cohort without MS (N=18,211), giving an estimated SMR of 1.68 (95%CI: 1.38-2.05). In a sensitivity analysis, EDSS-stratified SMRs were used from the Pokorski 1997 (1.6 (Mild), 1.84(Moderate), 4.44 (severe)).(5) This earlier study used a sample of 6727 MS patients from the Danish Multiple Sclerosis Registry, but the age and non-UK setting render this of limited value to decision making.

The NICE committee requested the EAG to run analyses informed by Harding 2018, which was a study on 2604 patients from the southeast Wales MS registry. (3) However, these SMRs are extremely high for higher EDSS states (Table 2). Stakeholder and committee feedback cast doubt on Jick 2014 and Harding 2018, as Jick 2014 does not distinguish between EDSS states while Harding 2018 suggests implausibly higher mortality at EDSS 8 or greater. In Sandoz point 8 SMRs of 2-3 are deemed plausible and a request is made for a pragmatic approach to SMRs. In Biogen point 4, a request is made for an approach that is partially informed by both Jick 2014 and Harding 2018.

In response to a direct request from NICE, the EAG have developed a pragmatic approach so that the average SMR across EDSS levels matched that of Jick 2014 and the differences between EDSS categories matched to Harding 2018.(3, 4) The calculation is illustrated for the average SMRs in Table 3 but the model itself samples SMRs on the log scale using Normal distributions with mean and SD in Table 2. As Harding 2018 reported SMRs only for EDSS≥4 we used the SMR from Jick 2014 for EDSS<4. The key step is calculating hazard ratios relative to an EDSS state where a majority of the cohort lie. The EAG made a pragmatic choice of EDSS=4 as based on a simulation of the DES for 100 patients and 100 samples (Table 4). This crudely gives SMRs that increase less rapidly than using Harding 2018 directly. A further modification was to assume the same SMRs in EDSS 8 and 9 as in EDSS 7 to avoid the extreme values; due to the very low proportions of the cohort in these EDSS categories (Table 4) this is not expected to have an impact on results.

We followed this approach on the log scale and using sampled SMRs, with uncertainty, from Jick 2014 and Harding 2018. This propagates uncertainty in the calculation through the probabilistic sensitivity analysis of the DES.

TABLE 2 MORTALITY SMR AND LOG (SMR) STRATEFIED BY SEVERITY, JICK 2014 AND HARDING 2018*

EDSS	0-4	4-5.5	6-6.5	7-7.5	8-8.5	9-9.5
SMR Jick 2014	1.68 (95% CI 1.38, 2.05)					
Log SMR (log SD) Jick 2014	0.52 (0.10)					
SMR (95% CI) Harding 2018	-	2.02 (0.98, 3.71)	3.86 (2.63, 5.47)	4.76 (2.82, 7.56)	22.17 (18.20, 26.75)	60.74 (47.62, 76.41)
Log SMR (log SD) Harding 2018	-	0.70 (0.34)	1.35 (0.19)	1.56 (0.25)	3.10 (0.10)	4.11 (0.12)

CI: Confidence Interval, SD: Standard Deviation, SMRL Standard Mortality Rate

*The economic model samples SMRs on the log scale using mean and SD in this table, but combined as in Table 3

TABLE 3 ILLUSTRATION OF SMR CALCULATIONS USING BOTH JICK 2014 AND HARDING 2018

EDSS	0	1	2	3	4	5	6	7	8	9
Pokorski (we don't use) SMR	1.6	1.6	1.6	1.6	1.84	1.84	1.84	4.44	4.44	4.44
Jick 2014 SMR	1.68	1.68	1.68	1.68	1.68	1.68	1.68	1.68	1.68	1.68
Harding for EDSS≥4 and otherwise Jick SMR	1.68	1.68	1.68	1.68	2.02	2.02	3.86	4.76	22.17	60.74
Harding relative to EDSS=4 Hazard ratios	0.83	0.83	0.83	0.83	1.00	1.00	1.91	2.36	10.98	30.07
Jick/Harding mix SMR	1.40	1.40	1.40	1.40	1.68	1.68	3.21	3.96	18.44*	50.52*

*In the model these SMRs are set equal to that in EDSS 7 due to their extreme values.

TABLE 4 PROPORTION OF TOTAL TIME AT RISK SPENT IN EACH EDSS CATEGORY ACROSS MODELLED TREATMENTS*

Jick (edss 0-9)	Edss 0	Edss 1	Edss 2	Edss 3	Edss 4	Edss 5	Edss 6	Edss 7	Edss 8	Edss 9
Natalizumab-IV	0.039	0.071	0.143	0.187	0.216	0.192	0.146	0.006	0.000	0.000
Natalizumab-SC	0.040	0.072	0.143	0.188	0.214	0.195	0.143	0.005	0.000	0.000
Natalizumab biosimilar-IV	0.043	0.078	0.142	0.181	0.212	0.193	0.144	0.005	0.000	0.000
Cladribine	0.043	0.069	0.142	0.179	0.205	0.201	0.154	0.006	0.000	0.000
Ofatumumab	0.042	0.075	0.146	0.181	0.217	0.190	0.143	0.006	0.000	0.000
Ocrelizumab	0.043	0.076	0.147	0.182	0.213	0.188	0.144	0.005	0.000	0.000

*This simulation used 100 patients and 100 samples and applied the Jick 2014 SMR across all EDSS categories.

2.2 Treatment with Ublituximab150mg

Estimated for the purposes of the analysis are the annual treatment, administration and monitoring costs for Ublituximab. The list price is £2,947, per 150 mg vial, treatment is initiated with 150 mg IV infusion, followed 450mg IV infusion 2 weeks later. Subsequent treatments are administer as 450mg IV infusions every 24weeks. Total annual treatment costs and assumed proportions of patents retreated after year 2 are listed in Table 5. Annual treatment administration and monitoring costs are listed in Table 6.

TABLE 5 ANNUAL TREATMENT ACQUISITION (LIST PRICES) QUANTITIES, COSTS AND PROPORTION OF PATIENTS RETREATED

Treatment	Year 1		Year 2 onwards		Patients treated (proportion)		
	Units (n)	Cost (£)	Units (n)	Cost (£)	Year 3	Year 4	Year 5+
ublituximab150 mg	10.13	£29,838.38	6.50	£19,155.50	0.75	0.75	0.75

TABLE 6 ANNUAL TREATMENT ADMINISTRATION & MONITORING COSTS

Treatment	Year 1		Year 2 onwards		Source
	Resource Use	Cost	Resource Use	Cost	
Annual Administration Costs					

Treatment	Year 1		Year 2 onwards		Source
	Resource Use	Cost	Resource Use	Cost	
Ublituximab150 mg	4 x day case (£626.13)	£2,504.52	2 x day case (£626.13)	£1252.26	AA30F Medical care of patients with multiple sclerosis, with CC score 0-1. Day case.(6)
Annual Monitoring Costs					
ublituximab150 mg	1x neurology (NCL) first visit (£195.74) 1 x MRI scan (£334)	£529.74	1x neurology (NCL) follow up visit (£184.23) 1 x MRI scan (£334)	£518.23	NCL 400 Neurology Service WF01A/B Non-Admitted Face-to-Face Attendance, First / Follow-up(6) RD07Z Magnetic Resonance Imaging Scan Requiring Extensive Patient Repositioning(6)

3 Committee base case

The Committee's preferred assumptions and analyses were based on the available evidence and included:

- Relevant comparators for natalizumab are Ocrelizumab (intravenous and subcutaneous), Ofatumumab, Cladribine and Ublituximab.
- EAG's base case NMAs for the outcomes ARR, CDP3, CDP6, SAEs, and stopping treatment to inform clinical efficacy
- Natural History of RRMS informed by time to event data from the MS Register in the UK.
- Assuming equal efficacy and safety of Natalizumab and Natalizumab biosimilar (CDP, ARR, Discontinuation, SAEs)
- Using the EAG's base-case assumption for treatment waning: baseline stopping rates from AFFIRM with treatment specific effects applied from NMA on the adverse events leading to withdrawal, but to explore more ways to model treatment wanning
- Using mortality data from Harding et al while noting the uncertainty in this estimate
- Including 6- weekly EID for 60% of people having Natalizumab and normal dosing for 40%, with the only impact being reduced costs on EID
- Excluding the costs of anti-JCV antibody testing for both natalizumab originator and biosimilar
- Assuming equal costs and resource use for subcutaneous and intravenous natalizumab

4 Updated EAG base case

The EAG's base case aligns with the committee base case, and is henceforth referred to as the EAG/Committee base case, but makes use of additional data and assumptions from

stakeholder feedback. HA RRMS from the MS Registry is used for baseline rates, all RRMS fixed effects from the NMA for treatment effects, an EDSS starting distribution from the MS Registry for HA RRMS, and costs for primary bands are used for comparator drugs.

The following assumptions are made:

- Interventions/comparators at 2nd line: Natalizumab-IV, Natalizumab-SC, Natalizumab biosimilar-IV, Natalizumab biosimilar-SC, Cladribine, Ofatumumab, Ocrelizumab, Ublituximab
- Available 3rd line treatments: Natalizumab-IV, Natalizumab-SC, Natalizumab biosimilar-IV, Natalizumab biosimilar-SC, Cladribine, Ofatumumab , Ocrelizumab, Ublituximab
- Proportions of patients on each of the 3rd line treatments follow estimates from the MS Registry (Table 1). Proportions on 4th or higher line are assumed equal across available therapies.
- Mortality follows average SMR from Jick 2014, with differences between EDSS state SMRs based on Harding 2018, and an assumption that the SMR EDSS 8 and 9 categories is equal to that for EDSS 7 (Section 2.1).(3, 4)
- EAG base case assumed treatment class effects
- Treatments not repeated after switching

Finally, a set of sensitivity analyses are conducted on the EAG/committee base case, as described in Table 7. These are in response to key uncertainties in the model highlighted by the committee and/or stakeholders (Section 1).

TABLE 7 SENSITIVITY/SCENARIO ANALYSES CONDUCTED ON THE EAG/COMMITTEE BASE CASE

Analysis	Description
Scenario 1. Sensitivity assuming a reduction in Natalizumab-SC administration costs	Reduces administration cost by a factor of 0.5x for Natalizumab-SC during year 1 to explore the company's assumption of reduced resource use (nurse administration hours per year). Increased capacity for service delivery at home(company funded) or in primary care setting.(7). Further assumes no further administrative costs from year 2 onwards to explore uptake of the company's at home injection service.
Scenario 2 assuming equal clinical effectiveness for natalizumab, ocrelizumab and ofatumumab.	Assumes cladribine is the only different treatment, as ocrelizumab and ofatumumab are assumed to be equally effective to Natalizumab, and ublituximab is assumed equivalent to ocrelizumab on the following clinical outcomes: CDP6, ARR, discontinuation due to SAEs, SAEs.
Scenario 3 exploring alternative ways to model treatment waning	Treatment effectiveness is assumed to wane over time by a reducing the treatment effects on relapsing and edss increase for RRMS patients. The waning effect is assumed to be 2% annually up to 5 years, 0% beyond 5 years.
Scenario 4 with all patients on subsequent treatment ocrelizumab	All patients on 3rd line treated with ocrelizumab. 4th or higher line patients treated where proportions are assumed equal across available therapies.
Scenario 5 with all patients on subsequent treatment ofatumumab	All patients on 3rd line treated with ofatumumab. 4th or higher line patients treated where proportions are assumed equal across available therapies.

Analysis	Description
Scenario 6 with all patients on subsequent treatment ublituximab	All patients on 3rd line treated with ublituximab. 4th or higher line patients treated where proportions are assumed equal across available therapies.
Scenario 7 using Jick/Harding mix for SMRs without setting SMR in EDSS 8/9 equal to that in EDSS 7	Mortality assumed to follow the Jick/Harding calibration without capping the SMR at EDSS7, which allows for greater uncertainty on EDSS 8 and 9.
Scenario 8 using lowest regional prices for alemtuzumab and cladribine (cPAS appendix only)	Uses lowest regional price for cladribine.
Scenario 9 using highest regional prices for alemtuzumab and cladribine (cPAS appendix only)	Uses highest regional price for cladribine.
Scenario 10 assuming Ocrelizumab SC has lower costs to Ocrelizumab IV	Ocrelizumab SC added as comparator and assumed clinically equivalent to Ocrelizumab IV. Ocrelizumab SC and Ocrelizumab IV have the same annual treatment cost, Ocrelizumab SC is administered 2x per year as per TA1025, thus annual administration costs are lower than Ocrelizumab IV.

5 Results

5.1 Base case results

The results of the analysis following the EAG/committee base case assumptions are provided in this section. We used 1000 samples and 1000 patients for this simulation. Uncertainty, as indicated by the 95% CrI is very high but general patterns can be seen.

The net benefit at £20,000/QALY and £30,000/QALY of natalizumab-IV, natalizumab-SC, and natalizumab biosimilar-IV are very similar, with 95% CrI that overlap. Mean values are greatest on natalizumab biosimilar-IV but the 95% CrI indicate no evidence of difference between the natalizumab strategies.

Ofatumumab, ocrelizumab and ublituximab have lower net benefits at £20,000/QALY and £30,000/QALY than the natalizumab strategies. The 95% CrI for incremental net benefits indicate evidence of greater net benefit on natalizumab-IV than on either of these comparators.

The mean net benefits of cladribine are higher than on natalizumab strategies. The 95% CrI for incremental net benefits relative to natalizumab-IV overlap with zero at both at £20,000/QALY, but most of the interval suggests greater net benefits on cladribine. Across treatments, cladribine has the greatest net monetary benefits at £20-30,000/QALY.

TABLE 8 NET BENEFIT AND INCREMENTAL NET BENEFIT IN FOR TREATMENTS IN COMPARISON TO NATALIZUMAB IV (PUBLIC LIST PRICES) FOR THE EAG/COMMITTEE BASE CASE (HARRMS)

Treatment	Net benefit at £20,000/QALY (95% CrI)	Net benefit at £30,000/QALY (95% CrI)	INB at £20,000/QALY (95% CrI)	INB at £30,000/QALY (95% CrI)	CEAC at £20,000/QALY	CEAC at £30,000/QALY
Natalizumab-IV **(Reference)**	-130,861.12 (-181,613.34, -87,794.06)	-39,649.31 (-107,550.58, 15,288.45)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.009	0.013
Natalizumab-SC	-131,026.69 (-181,566.78, -88,552.20)	-39,751.32 (-105,181.61, 14,865.38)	-165.57 (-14,743.07, 13,501.72)	-102.01 (-16,166.73, 15,876.77)	0.011	0.014
Natalizumab biosimilar-IV	-123,351.43 (-174,540.99, -81,810.89)	-32,171.08 (-101,578.76, 21,424.88)	7,509.69 (-5,963.52, 23,290.52)	7,478.23 (-7,742.25, 25,159.92)	0.051	0.063
Cladribine	-82,559.61 (-145,405.42, -25,426.32)	7,750.91 (-74,974.46, 83,263.78)	48,301.51 (-378.89, 115,101.49)	47,400.22 (-3,103.75, 115,127.07)	0.929	0.91
Ublituximab	-157,833.25 (-209,333.39, -113,931.74)	-67,034.85 (-139,422.70, -10,363.54)	-26,972.13 (-40,260.93, -12,971.01)	-27,385.54 (-42,504.95, -11,563.35)	0	0
Ofatumumab	-150,357.94 (-200,662.26, -102,622.26)	-60,747.44 (-124,868.53, -1,718.88)	-19,496.82 (-37,077.69, -3,443.26)	-21,098.14 (-41,773.43, -990.09)	0	0
Ocrelizumab	-160,453.38 (-216,534.29, -107,357.60)	-69,636.12 (-137,506.06, -4,952.17)	-29,592.26 (-54,284.80, -7,980.74)	-29,986.82 (-54,989.18, -7,088.72)	0	0

The total costs and QALYs for all included treatments, and their incremental comparison with Natalizumab-IV, are provided in Table 9. The 95% CrI for both costs and QALYs are wide, suggesting high uncertainty.

Natalizumab-SC, natalizumab biosimilar-IV, and cladribine have lower costs than natalizumab-IV but only the 95% CrI for incremental costs for cladribine excludes 0.0 indicating that there is only evidence that cladribine has lower costs. Ofatumumab, ocrelizumab, and ublituximab have higher mean costs and the 95% CrI for the incremental costs excludes 0.0 indicating evidence of a difference. The 95% CrI for QALYs are overlapping suggesting no difference, although the mean QALYs are lower on all treatments than on natalizumab-IV with the exception of natalizumab-SC.

The natalizumab biosimilar-IV has lower costs but also lower QALYs than natalizumab-IV. However, the differences in costs and QALYs are uncertain with 95% CrI overlapping, suggesting no evidence of a difference in costs or QALYs. Natalizumab-SC has very similar costs and QALYs to natalizumab-IV.

Across treatments, total costs are lowest on cladribine and QALYs are highest on natalizumab-IV and natalizumab-SC.

ICERs comparing the natalizumab-IV to each of the other treatments are provided for completeness, but decision making should focus on the incremental net benefits as they better capture the high degree of uncertainty in this analysis. We see that ofatumumab, ocrelizumab and ublituximab are dominated by natalizumab-IV. In all other cases, the costs and QALYs of natalizumab-IV are higher and the ICER is above £20-30,000/QALY, suggesting it is not cost-effective against natalizumab-SC, natalizumab biosimilar-IV, or cladribine.

TABLE 9 TOTAL AND INCREMENTAL COSTS AND QALYS AND ICERS FOR NATALIZUMAB IV IN COMPARISON TO TREATMENTS (PUBLIC LIST PRICES) FOR THE BASE CASE (HARRMS)

Treatment	Total costs £ (95% CrI)	Total QALYs (95% CrI)	Incremental costs £ (95% CrI)	Incremental QALYs (95% CrI)	ICER (£/QALY)*
Natalizumab-IV **(Reference)**	314,000.26 (271,332.05, 367,455.98)	9.11 (6.72, 11.35)	-	-	-
Natalizumab-SC	313,284.75 (268,953.10, 366,567.46)	9.12 (6.70, 11.32)	292.69 (-12,990.49, 14,232.12)	0.0064 (-0.38, 0.39)	46,050
Natalizumab biosimilar-IV	313,577.44 (271,195.19, 364,831.48)	9.13 (6.62, 11.38)	-7,572.61 (-22,238.11, 6,467.29)	-0.0031 (-0.40, 0.38)	2,406,985
Cladribine	305,712.14 (265,346.48, 358,016.73)	9.12 (6.66, 11.29)	-50,104.09 (-115,643.25, -4,504.95)	-0.09 (-0.52, 0.32)	555,915
Ublituximab	263,180.66 (225,879.11, 306,731.65)	9.03 (6.56, 11.19)	26,145.30 (14,904.12, 38,765.33)	-0.041 (-0.44, 0.35)	Natalizumab-IV dominant
Ofatumumab	339,430.05 (294,724.31, 392,799.32)	9.08 (6.46, 11.28)	16,294.19 (3,322.22, 31,994.59)	-0.16 (-0.69, 0.30)	Natalizumab-IV dominant
Ocrelizumab	329,578.94 (280,980.23, 386,275.56)	8.96 (6.45, 11.11)	28,803.16 (9,238.05, 54,874.55)	-0.039 (-0.45, 0.36)	Natalizumab-IV dominant

*‡located in South West (SW) quadrant of cost-effectiveness plane. *Not reported if natalizumab-IV is Dominant or Dominated*

The cost-effectiveness plane and CEAC are presented in Figure 1 and Figure 2, respectively. The cost-effectiveness plane graphically illustrates the high uncertainty in incremental costs and effects of Table 9. It also makes it clear that natalizumab-IV is very unlikely to be cost-effective at a £30,000/QALY willingness-to-pay threshold compared to any of the treatments. The CEAC confirms the finding that cladribine is most likely to be cost-effective in the £20-30,000/QALY range. These CEAC values at £20,000/QALY and £30,000/QALY are also reported in Table 8.

FIGURE 1 COST-EFFECTIVENESS PLANE FOR TREATMENTS IN COMPARISON TO NATALIZUMAB IV, WTP £30,000/QALY (PUBLIC LIST PRICES) FOR THE BASE CASE (HARRMS)

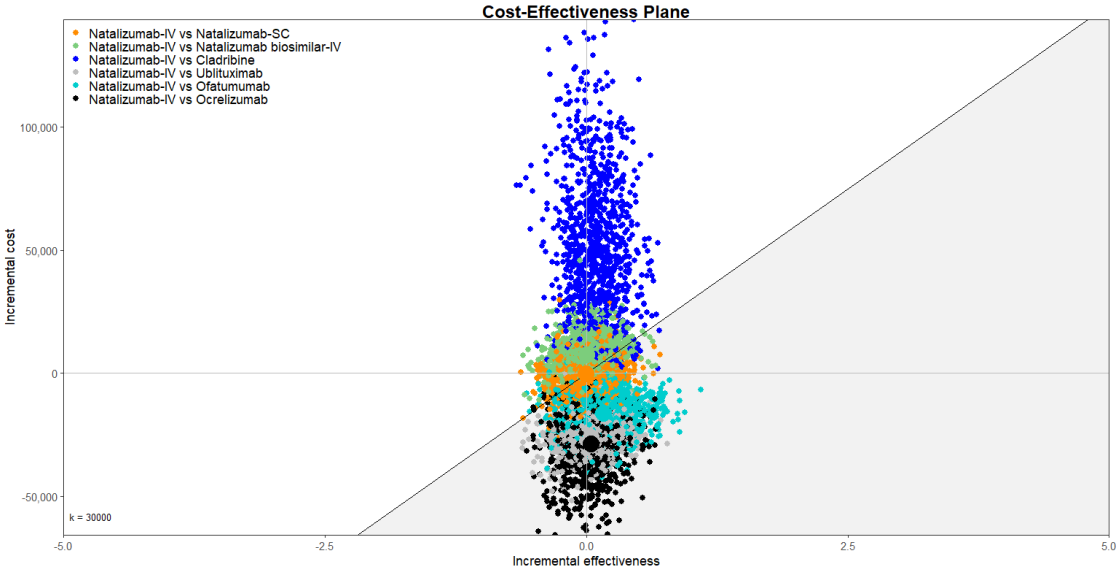
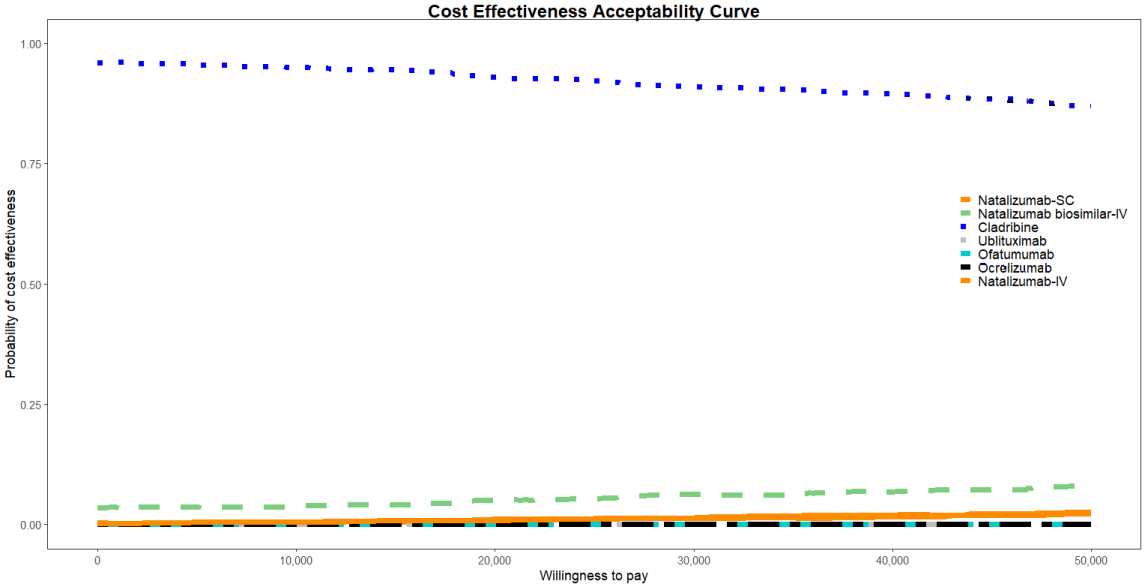


FIGURE 2 COST EFFECTIVENESS ACCEPTABILITY CURVE FOR TREATMENTS IN COMPARISON TO NATALIZUMAB IV, WTP £30,000 (PUBLIC LIST PRICES)



5.2 Sensitivity analyses results

The incremental net benefits from the sensitivity analyses at £20,000/QALY are presented in Table 10 and at £30,000/QALY in Table 11. We used 100 samples and 100 patients for these simulations.

These sensitivities again find that natalizumab-IV has lower net benefit at £20-30,000/QALY than natalizumab biosimilar-IV with very little impact on the mean results. The 95% CrI overlap with 0.0 in all scenarios, suggesting no evidence of a difference. Cladribine is found to have the greatest net benefit at £20-30,000/QALY across all scenarios, again with little impact on the results, and again with 95% CrI that overlap with 0.0 suggesting no evidence of a difference. Natalizumab strategies have greater net benefit than ofatumumab, ocrelizumab and ublituximab in all scenarios. Unlike in the base case, the 95% CrI for these comparators relative to natalizumab-IV overlap with 0.0 in all scenarios suggesting uncertainty around the base case finding of greater net benefit.

TABLE 10 INCREMENTAL NET BENEFITS RELATIVE TO NATALIZUMAB-IV AT £20,000/QALY FOR THE BASE CASE AND SENSITIVITY ANALYSES (PUBLICLY AVAILABLE LIST PRICES)

Treatment	Base case	Scenario 1 (reduction in Natalizumab-SC administration costs)	Scenario 2 (equal clinical effectiveness for natalizumab, ocrelizumab and ofatumumab)	Scenario 3 (treatment wanning)	Scenario 4 (subsequent treatment with ocrelizumab)
Natalizumab-SC	-165.57 (-14,743.07, 13,501.72)	36,845.00 (-1,387.85, 80,467.66)	2,747.10 (-35,729.39, 30,744.78)	-1,769.33 (-30,631.38, 31,304.92)	-1,766.51 (-35,424.74, 24,653.62)
Natalizumab biosimilar-IV	7,509.69 (-5,963.52, 23,290.52)	8,418.34 (-20,894.33, 42,752.58)	6,348.55 (-31,275.90, 37,867.81)	7,141.32 (-27,271.56, 43,952.09)	5,448.47 (-23,836.50, 38,942.14)
Cladribine	48,301.51 (-378.89, 115,101.49)	49,904.46 (-530.25, 115,842.83)	43,576.70 (-6,999.56, 109,903.78)	44,913.13 (-6,766.88, 110,839.23)	44,718.21 (-5,148.15, 99,509.15)
Ublituximab	-26,972.13 (-40,260.93, -12,971.01)	-24,262.71 (-49,046.88, 7,978.45)	-26,299.40 (-57,242.06, 1,262.95)	-27,167.07 (-60,014.21, 1,620.70)	-28,709.47 (-62,833.28, 4,214.29)
Ofatumumab	-19,496.82 (-37,077.69, -3,443.26)	-17,764.21 (-56,003.86, 16,221.17)	-14,300.46 (-48,091.07, 14,870.57)	-19,685.63 (-55,422.73, 14,934.03)	-23,403.14 (-51,976.26, 2,208.22)
Ocrelizumab-IV	-29,592.26 (-54,284.80, -7,980.74)	-27,699.97 (-69,461.81, 4,240.18)	-25,933.67 (-58,133.16, 4,519.41)	-30,773.98 (-69,046.57, 7,198.09)	-32,557.44 (-76,147.94, 2,989.72)

Treatment	Scenario 5 (subsequent treatment with ofatumumab)	Scenario 6 (subsequent treatment with ublituximab)	Scenario 7 (Jick/Harding mortality not capped at EDSS7)	Scenario 10 (Ocrelizumab SC added as a comparator with lower annual administration costs than Ocrelizumab IV)*
Natalizumab-SC	132.65 (-31,936.58, 27,652.30)	112.42 (-29,538.95, 29,907.52)	-753.85 (-26,891.53, 29,316.24)	TBC
Natalizumab biosimilar-IV	3,753.21 (-22,334.08, 38,248.94)	5,615.30 (-33,724.98, 45,566.14)	5,968.16 (-27,290.40, 34,581.92)	TBC
Cladribine	47,579.76 (-16,588.90, 114,142.03)	49,467.38 (-12,386.90, 122,701.39)	43,054.68 (-4,893.61, 95,635.69)	TBC
Ublituximab	-26,526.30 (-50,318.47, 351.12)	-27,010.89 (-59,852.94, 5,514.18)	-28,083.05 (-53,874.66, 2,524.86)	TBC
Ofatumumab	-18,847.71 (-51,518.19, 16,038.95)	-19,243.41 (-55,089.85, 21,405.40)	-18,404.60 (-56,857.21, 11,695.23)	TBC
Ocrelizumab-IV	-27,691.15 (-54,923.57, 3,092.56)	-28,949.01 (-60,933.75, 5,649.46)	-28,065.81 (-62,761.47, 17,666.24)	TBC
Ocrelizumab-SC	-	-	-	TBC

*Error in list prices analysis so results only provided using confidential prices in confidential appendix.

TABLE 11 INCREMENTAL NET BENEFITS RELATIVE TO NATALIZUMAB-IV AT £30,000/QALY FOR THE BASE CASE AND SENSITIVITY ANALYSES (PUBLICLY AVAILABLE LIST PRICES)

Treatment	Base case	Scenario 1 (assuming a reduction in Natalizumab-SC administration costs)	Scenario 2 (equal clinical effectiveness for natalizumab, ocrelizumab and ofatumumab)	Scenario 3 (treatment wanning)	Scenario 4 (subsequent treatment with ocrelizumab)
Natalizumab-SC	-102.01 (-16,166.73, 15,876.77)	36,094.49 (-11,962.64, 82,752.51)	3,348.80 (-46,945.74, 36,247.52)	-2,926.31 (-40,750.13, 36,197.95)	-2,553.63 (-44,101.44, 35,209.41)
Natalizumab biosimilar-IV	7,478.23 (-7,742.25, 25,159.92)	7,930.89 (-29,705.74, 52,307.19)	5,019.76 (-41,291.75, 42,901.41)	6,673.87 (-31,066.96, 45,488.13)	3,694.04 (-34,109.88, 42,700.39)
Cladribine	47,400.22 (-3,103.75, 115,127.07)	49,014.83 (-14,091.67, 114,757.50)	42,210.14 (-16,356.45, 113,713.22)	43,113.37 (-17,914.47, 105,440.32)	42,509.34 (-11,129.78, 99,664.79)
Ublituximab	-27,385.54 (-42,504.95, -11,563.35)	-25,035.77 (-60,728.22, 11,811.29)	-27,472.69 (-61,572.26, 9,046.03)	-28,029.50 (-69,864.93, 12,459.49)	-30,080.59 (-70,921.79, 15,890.49)
Ofatumumab	-21,098.14 (-41,773.43, -990.09)	-19,812.91 (-65,128.28, 24,029.28)	-14,788.72 (-53,295.19, 20,908.58)	-22,321.46 (-66,477.88, 21,631.47)	-27,087.22 (-69,055.38, 11,617.82)
Ocrelizumab-IV	-29,986.82 (-54,989.18, -7,088.72)	-27,735.97 (-73,555.88, 9,294.62)	-26,065.01 (-63,672.49, 13,068.61)	-31,619.67 (-79,653.07, 19,888.99)	-33,280.67 (-77,382.03, 10,127.16)

Treatment	Scenario 5 (subsequent treatment with ofatumumab)	Scenario 6 (subsequent treatment with ublituximab)	Scenario 7 (Jick/Harding mortality not capped at EDSS7)	Scenario 10 (Ocrelizumab SC added as a comparator with lower annual administration costs than Ocrelizumab IV)*
Natalizumab-SC	-167.61 (-38,514.44, 41,193.17)	-560.50 (-36,791.26, 40,564.42)	-660.81 (-31,745.05, 41,727.17)	TBC
Natalizumab biosimilar-IV	1,645.97 (-37,506.53, 41,637.62)	3,412.96 (-46,095.94, 51,125.12)	5,257.25 (-39,177.34, 41,373.85)	TBC
Cladribine	46,810.14 (-30,561.88, 116,547.37)	47,990.60 (-17,517.79, 124,212.31)	42,359.44 (-8,876.11, 102,662.19)	TBC
Ublituximab	-26,787.08 (-56,886.83, 7,407.07)	-27,993.35 (-68,294.82, 12,723.50)	-28,541.05 (-60,464.98, 12,707.44)	TBC
Ofatumumab	-20,556.50 (-62,847.40, 22,985.73)	-21,817.17 (-60,915.86, 31,375.89)	-19,291.03 (-67,149.53, 21,200.17)	TBC
Ocrelizumab-IV	-27,697.06 (-62,449.42, 9,762.84)	-29,774.70 (-66,931.27, 17,508.37)	-27,881.92 (-70,844.52, 28,350.33)	TBC
Ocrelizumab-SC	-	-	-	TBC

*Error in list prices analysis so results only provided using confidential prices in confidential appendix.

5.3 Additional outputs from the model

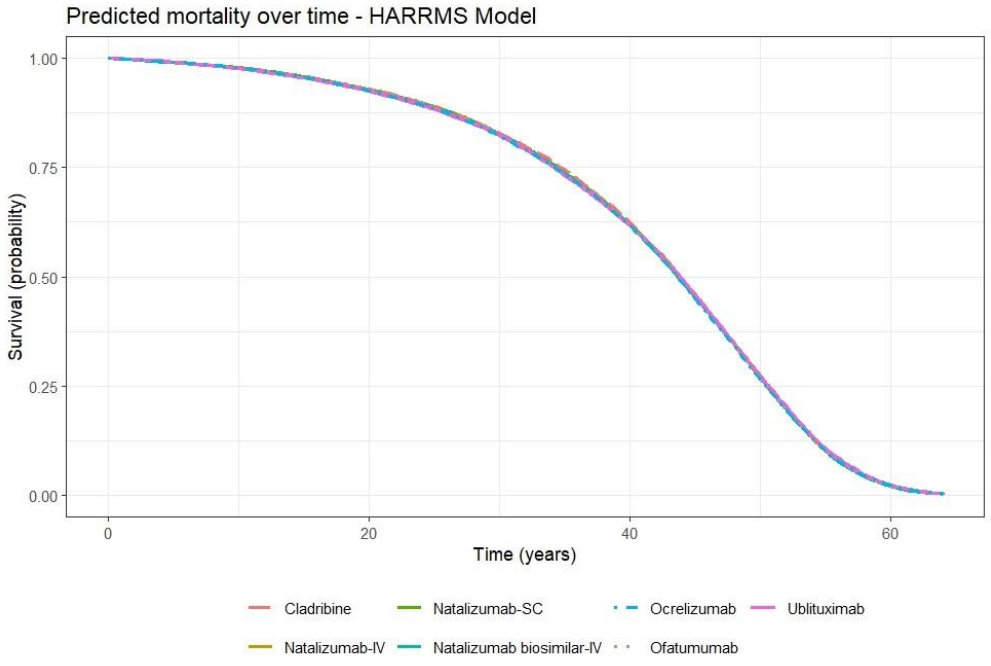
To assist in checking face validity of the model outputs, the EAG have generated additional outputs from the EAG/committee base case. The first is the proportion of people with secondary-progressive MS in the model at 5, 10 and 15 years (Table 12). No direct treatment effect is assumed on rates of progression to SPMS and this is illustrated with the very similar percentages in SPMS. The rate of progression to SPMS is affected by current EDSS, progression of which is affected by treatment, but over a 5-15 year time period this is also affected by subsequent treatment.

The second additional output are survival curves for each of the treatment strategies (Figure 3). There is also no direct treatment effect on mortality but it is affected by the EDSS-dependent SMRs (Section 2.1). However, as in the progression to SPMS, the impact is too small to make a detectable difference in survival curves between treatments.

TABLE 12 PROPORTIONS OF PATIENTS WITH SECONDARY PROGRESSIVE MULTIPLE SCLEROSIS OVER TIME AT 5, 10 AND 15 YEARS

	5 years	10 years	15 years
Natalizumab-IV	27.7%	42.3%	50.6%
Natalizumab-SC	27.7%	42.3%	50.5%
Natalizumab biosimilar-IV	27.6%	42.1%	50.2%
Cladribine	27.6%	41.9%	49.7%
Ublituximab	27.6%	42.2%	50.3%
Ofatumumab	27.7%	42.2%	50.4%
Ocrelizumab	27.6%	42.0%	49.9%

FIGURE 3 PREDICTED MORTALITY OVER TIME BY TREATMENT



Appendix: Collated comments from consultation

Comments from Sandoz

Comment number	Comments	EAG response
1	While Sandoz were disappointed that the Committee were unable to recommend natalizumab at their first meeting, we recognise that this was due to the lack of appropriate analyses presented by the Assessment Group to align with the Committee preferences, and are hopeful that a second meeting will allow the Committee to recommend natalizumab within its licensed indication.	Following the meeting, the EAG provided analyses using the preferences specified by the committee and these informed the decision. See Section 3 and Section 4 for the updated EAG/Committee base case.
2	Sandoz welcome and agree with the following Committee conclusions in the draft guidance: • Para 3.1 – that RRMS can have a substantial impact of quality of life • Para 3.2 – that natalizumab would be a welcome additional treatment option • Para 3.3 – that ocrelizumab (s.c. and i.v.), ofatumumab and ublituximab are relevant comparators (see below for our comments on cladribine); and that all other DMTs noted in the final NICE scope are not relevant comparators • Para 3.4 – that natalizumab improves disease control in people with highly active RRMS • Para 3.5 – that counselling and anti-JCV testing is a routine part of practice when using natalizumab • Para 3.9 – that the approach to comparative treatment effectiveness is acceptable for decision making • Para 3.12 – that it is appropriate to assume clinical equivalence between originator and biosimilar • Para 3.15 – that DMTs are stopped at EDSS 7 • Para 3.17 – that the EAG utility values are appropriate • Para 3.18 – that 60% of patients receiving natalizumab in the NHS receive extended interval dosing • Para 3.19 – that anti-JCV testing costs be excluded from the economic model	No EAG response needed.

Comment number	Comments	EAG response
	• Para 3.20 – that it is appropriate to model equivalent resource use for s.c. and i.v. routes of administration	
3	Sandoz agree in part with the following Committee conclusions but provide further comments to be considered at the second committee meeting: • Para 3.3 – that cladribine is a relevant comparator: Sandoz accept that cladribine is licensed, reimbursed and used to some degree in the NHS for the patient population covered by this appraisal, however Sandoz understand from commercially available market research data that cladribine use (in all positions) is low in the NHS and request that the Committee consider whether cladribine could for practical purposes be considered immaterial to the appraisal, which would therefore support Sandoz' proposal for a cost comparison of the high efficacy monoclonal antibody DMTs. Sandoz would note that analysis from the global MSBase cohort have demonstrated that cladribine is less effective than the most potent intravenous MS therapies, including natalizumab (Roos et al 2024. Available to download free-of-charge https://journals.sagepub.com/doi/10.1177/13524585241267211). Sandoz would also note that, unlike natalizumab, cladribine is contraindicated in pregnancy and breast feeding. • Para 3.6 – that the EAG's NMA is appropriate for decision making; Sandoz considers this a practical conclusion in the context of the conclusion on comparators in para 3.3 but notes that the EAG's NMA was open to criticism, as we have previously commented on. • Para 3.7 – that a cost comparison of ocrelizumab, ofatumumab and natalizumab could be informative but that ublituximab and cladribine were also relevant; having initially proposed the cost comparison approach, Sandoz would suggest further expanding it to include ublituximab alongside ocrelizumab and ofatumumab and, as noted above, Sandoz request that the Committee reconsider how material cladribine is for this appraisal. Such an analysis would logically extend the approach taken by the Committee in TA1025 where ublituximab was recommended on the basis of cost comparison with ofatumumab and ocrelizumab. • Para 3.8 – that the EAG's DES model is appropriate for decision making; Sandoz consider the EAG's DES model to be overly complex, lacking in transparency and to be so computationally inefficient to run that it forms a barrier to effective participation by consultees, nonetheless Sandoz are willing to proceed with participation in the appraisal given the many positive Committee conclusions welcomed above. As noted elsewhere in this response, Sandoz continue to consider that a cost comparison approach versus the relevant high efficacy	See sections 1.1, 1.2, 1.4, and 1.10

Comment number	Comments	EAG response
	monoclonal antibody DMTs identified by the Committee would be the most practical economic analysis. • Para 3.10 – the Committee identified the source of natural history data as being a source of uncertainty in the appraisal; Sandoz reiterate that a cost comparison approach, as justified above, would avoid this source of uncertainty and thus be preferable for decision making, given the committee's many positive conclusions welcomed above. • Para 3.11 – similar to our comment on para 3.10, Sandoz reiterate that a cost comparison approach, as justified above, would avoid this source of uncertainty and thus be preferable for decision making, given the committee's many positive conclusions welcomed above. • Para 3.13 – similar to our comment on para 3.10, and 3.11, Sandoz reiterate that a cost comparison approach, as justified above, would avoid this source of uncertainty and thus be preferable for decision making, given the committee's many positive conclusions welcomed above. • Para 3.14 – similar to our comment on para 3.10, 3.11 and 3.13, Sandoz reiterate that a cost comparison approach, as justified above, would avoid this source of uncertainty and thus be preferable for decision making, given the committee's many positive conclusions welcomed above. • Para 3.15 – similar to our comment on para 3.10, 3.11, 3.13 and 3.14, Sandoz reiterate that a cost comparison approach, as justified above, would avoid this source of uncertainty and thus be preferable for decision making, given the committee's many positive conclusions welcomed above.	
4	In response to the Committee's requests for additional input and analysis from the Companies in Para 3.23 for "Any relevant information regarding clinical equivalence of originator and biosimilar": • Guidance on the licensing of biosimilar products - GOV.UK: "Once authorised, a biosimilar product is considered to be interchangeable with their RMP, which means a prescriber can choose the biosimilar medicine over the RMP (or vice versa) and expect to achieve the same therapeutic effect. Likewise, a biosimilar product is considered to be interchangeable with another biosimilar to the same RMP. As a result of interchangeability, switching patients from one product to another (RMP or biosimilar) has become clinical practice. The decision rests with the prescriber in consultation with the patient, in line with the principles of shared decision making; both need to be aware of the brand name of the product received. "	We do not consider this additional evidence that could inform our appraisal.

Comment number	Comments	EAG response
	• NICE position statement on biosimilars in appraisals: "Recommendations will refer to the British approved name of the medicine and will not differentiate between the originator and biosimilar products. The guidance will state that treatment should be initiated with the cheapest available product. In acknowledgment of the fact that the EMA does not make recommendations on whether a biosimilar should be used interchangeably with its reference medicine, or with other biosimilar medicines, the issue of switching and interchangeability will not be considered within the technology appraisal."	

5	In response to the Committee's requests for additional input and analysis from the Companies in Para 3.23 "A scenario assuming clinical equivalence for natalizumab, ocrelizumab and ofatumumab"
	
	• Sandoz have updated their cost comparison analysis from their original evidence submission to align with the committee preference on:
	  ○ adding ublituximab as a comparator
	  ○ considering s.c. ocrelizumab in addition to i.v.
	  ○ assuming 60% of patients receive natalizumab extended interval dosing
	  ○ to assume equal resource use for s.c. and i.v. for DMTs administered in hospitals, namely a Day Case cost for AA30F from the NHS Cost Collection
	  ○ to update the cost used for hospital administration to the latest published NHS Cost Collection for 2023/24, which was published after the original Sandoz evidence submission
	• The results of this analysis, undertaken over a three-year time horizon, show that natalizumab biosimilar has the lowest modelled cost for all comparators at list price.
	• Given the need for NICE to undertake analyses at the confidential NHS prices of all DMTs, Sandoz has provided a working CMM model in Excel with built-in functionality for NICE to undertake these analyses themselves using the Sandoz model.
	• Sandoz request that results incorporating confidential NHS prices produced by NICE from the Sandoz CMM are presented to the Committee at the Committee meeting independently of any EAG analyses.
		See section 1.1 for discussion of the submitted cost-comparison. The EAG have re-run the cost comparison using confidential discount prices and provided these to NICE in a confidential appendix.

6	In response to the Committee's requests for additional input and analysis from the Companies in Para 3.23 "Exploring alternative ways to model treatment waning":	The EAG have consulted with clinical advisers and provide a response in Section 1.5.

Comment number	Comments	EAG response
	• A clinical expert consulted by Sandoz during the DG consultation was of the opinion that the treatment effect of a DMT is binary, either it works or does not work and discussing treatment waning in MS is not helpful. • Sandoz are concerned that conceptual arguments on waning of treatment effect are inherently uncertain and not amenable to evidence; in the context of the cost of natalizumab reducing to biosimilar pricing levels following loss of exclusivity, Sandoz request that Committee consider the decision problem at hand pragmatically.	
7	In response to the Committee's requests for additional input and analysis from the Companies in Para 3.23 "Data on subsequent treatments in NHS clinical practice": • Sandoz firstly note that the Committee request for evidence on the split of subsequent treatments between ublituximab, ocrelizumab and ofatumumab cannot be answered with evidence from NHS practice, given that ublituximab was only recommended by NICE on 18th December 2024, with a 30-day implementation period ending on 17th January 2024. As such, there have only been two months of availability on the NHS which is insufficient time to reach a new equilibrium in prescribing practice. • Sandoz suggest that this is pragmatically addressed with a set of scenario analyses assuming 100% usage of each of ublituximab, ocrelizumab and ofatumumab to determine whether this uncertainty is of material relevance to any ICER produced by the EAG model.	See section 1.6
8	In response to the Committee's requests for additional input and analysis from the Companies in Para 3.23 "Exploring alternative ways to model mortality": • A clinical expert consulted by Sandoz during the DG consultation was of the opinion that the Harding data (Harding et al 2018) gives unrealistic increases in mortality rate with increased EDSS scores. Other data sets suggest the risk goes up 2–3 times which is much more realistic. • As such, Sandoz consider that the Committee should adopt a pragmatic approach to this issue and consider calibrating between sources to derive SMRs that do increase with EDSS but where that increase is more realistic than the Harding data	The EAG have take the pragmatic approach suggested by the manufacturer and details are provided in Section 1.9 and Section 2.1.

Comment number	Comments	EAG response
9	In response to the Committee's requests for additional input and analysis from the Companies in Para 3.23 "Data on the proportion of people having 6-weekly dosing in NHS clinical practice": • Sandoz welcome the Committee's conclusion on 60% usage of extended interval dosing • A clinical expert consulted by Sandoz during the DG consultation was of the opinion that EID was expected to become more and more common over time to control PML risk	See section 1.7

Comments from Biogen

Comment number	Comments	EAG response
1	The Company is concerned that the economic conclusion in the Draft Guidance doesn't take into account the potential workload savings and reduction in NHS and patient burden associated with the SC formulation of natalizumab-TYS. SC natalizumab-TYS – administered through the Tysabri Home Injection service (THIS) provided by the Company – enables care closer to home, minimises patient travel time required for treatment, helping to address inequalities and reduces patient costs and administration time (e.g., transport, childcare, lost productivity). When administered in a secondary care setting, cost savings to the NHS include reduction in HCP time, infusion chair time, and equipment costs. Increased infusion suite capacity also allows more MS patients to be treated reducing waiting lists. This was detailed in the Company's initial submission to NICE, and in subsequent communications with NICE and the EAG. The Company disagrees with the conclusion in the Draft Guidance that "the overall time saving with subcutaneous natalizumab [is] minimal". Silingardi et al. 2023 showed in a time and motion study in Salford that when administered in a secondary care setting, SC natalizumab-TYS provided DMT treatment total savings of 1 h 32 min in the SC cohort compared with IV administered cohort (see CS section B.2.6.1, pg. 55).[1] Similar time and resource saving were reported through a survey of clinicians and patients treated at Morriston Hospital, Swansea, which showed an average combined infusion and surveillance time for IV natalizumab-TYS of 142 minutes, reducing to an average of 61 minutes for SC natalizumab-TYS.[2] A model developed by the Company to estimate costs and time savings for switching from IV to SC estimates that switching 500 patients results in hospital chair time savings of [redacted], nurse/pharmacy time savings of [redacted] and total cost savings of [redacted].[3] SC also provides direct patient benefits. In the Nova (Part 2 study), the majority of patients on Q6W dosing preferred SC vs. IV and 82.9% of patients cited the key reason as "requiring less time in clinic" (see EAG report consultation response form pg. 7).[4] Similarly, the TONiC study highlighted all but one patient who switched from IV to SC expressed either a "fairly strong" or "very strong" preference for SC vs IV driven by time savings (see CS section B.2.6.1, pg. 56).[5] Survey data from Morristown Hospital, Swansea showed that 96% of the 64 patients who had switched to SC natalizumab-TYS from IV, or who initiated the SC formulation, were "satisfied" or "very satisfied" with switching. TONiC also showed that 39.8% of patients with MS travelled between 1 to 2 hours, 8% travelled 2 to 4 hours and 3.5% travelled over 4 hours for MS treatment administration, further showing the advantages of care closer to home.[5] The Tysabri Home Injection Service (THIS) provided by the Company includes delivery of natalizumab-TYS and Biogen-funded homecare nurse for administration, which provides both cost savings and potential VAT	The EAG have considered this feedback in Section 1.8 and conducted a sensitivity analysis on the new EAG/Committee base case.

Comment number	Comments	EAG response
	savings (EAG report consultation response form pg. 7). The first patient was administered SC natalizumab-TYS via THIS in [redacted], and new patient registrations, and overall patient numbers are [redacted] (Figure 4). The Company expects this [redacted] for the THIS program to continue based on the associated time and cost savings with [redacted] of unit SC sales under the program within 6 months, peaking at around [redacted]. **Figure 4 New registrations and total patient numbers for the Tysabri Home Injection Service programme (as of February 2025)** [redacted] The Company appreciates that Committee discussion explored the issue of continued availability of homecare-related services that are provided by manufacturers, and that ongoing patient monitoring may be more challenging in care settings outside of secondary care. Regarding ongoing provision of services, the Company wants to highlight its long-standing commitment to supporting these services in the UK across our MS portfolio (including for products with loss of exclusivity), and that the [redacted] should further alleviate these concerns. Regarding patient monitoring and safety, the Company would like to add that there are robust measures in place to monitor the risk of PML for patients enrolled onto THIS. Patients receiving treatment with natalizumab-TYS already possess a Patient Alert Card which contains important safety information that they need to be aware of before, during and after stopping treatment. In addition, the patients receive treatment by a healthcare professional (nurse) in their homes when they are enrolled onto THIS. The nurse goes through a comprehensive "outside of clinical setting" (OCS) checklist with the patient before each administration of	

Comment number	Comments	EAG response
	natalizumab-TYS. This checklist has been reviewed and approved by the MHRA and is part of the risk management materials for natalizumab-TYS. It includes a decision tree for the healthcare professional to make a decision every time whether to administer treatment and involves close monitoring of any symptoms suggestive of PML. Similar robust measures will also be in place for [redacted] The Company firmly believes that any decision that does not take into account the benefits of the SC formulation of natalizumab-TYS is not reflecting the true value of the therapy.	
2	Related to Comment 1, the Company does not believe that the following statement is factually accurate: ""The committee noted that subcutaneous administration of natalizumab was declining and clinical expert opinion is that home administration is rarely used in the NHS." The clinical experts at the meeting did not state this, instead they articulated that within their respective centres approximately 30-40% of natalizumab patients receive SC natalizumab-TYS, however due to a strict drugs committee within their centres, no further patients are allowed to switch from IV to SC administration. These experiences are not representative of all centres prescribing natalizumab. Unit sale data for natalizumab-TYS indicates that SC natalizumab-TYS use is increasing, not declining, and it now represents ~[redacted]% of overall natalizumab-TYS unit sales.	No EAG response needed.
3	The Final Guidance notes the uncertainty regarding natalizumab-TYS dosing in clinical practice, given the ability to use Extended Interval Dosing (EID). EID use in clinical practice has been confirmed by the Company with UK clinicians, both prior to dossier submission and after the Committee meeting. Company data shows that the average number of doses of natalizumab-TYS per patient per year is [redacted], not 13 as would be the case for Standard Interval Dosing [SID]). The Company agrees with the Committee's position that approximately 60% of patients receiving natalizumab in clinical practice would do so with an EID regimen. The Company believes that the evidence to date does not indicate any difference in efficacy or safety for natalizumab-TYS IV vs. SC, and the proportion of patients receiving both formulations via EID in the future is expected to be the same. Indeed, results from the natalizumab observational program presented at the European Academy of Neurology in 2024 show that efficacy was similar in patients switching from IV to SC formulation, regardless of SID or EID dosing (see CS section B.2.5.3.1, pg. 49). More generally, feedback from clinical experts to the Company suggests that EID is used routinely in clinical practice and that it also provides clinicians with the flexibility they need in deciding on appropriate therapy. Q6W dosing of SC natalizumab-TYS is particularly important for pregnant women and those with JCV-positivity, and feedback to the Company is that of the approximately 3 in every 4 patients receiving natalizumab who get SC Tysabri (vs the remaining 25% who receive IV natalizumab) at least two thirds are on	See section 1.7. The EAG have followed committee recommendations on EID which align with calculations by the manufacture.

Comment number	Comments	EAG response
	6-weekly dosing. Feedback to the Company from clinical experts is that EID is particularly valuable for patients who are pregnant, JCV-positive or have been on treatment for more than 2 years. Q8W dosing provides further dose frequency flexibility to support, for instance, maintaining outcomes during pregnancy. Overall, EID for natalizumab-TYS IV/SC (Q6W/Q8W) used in routine clinical practice in the UK and is associated with multiple benefits, namely: 1) cost savings due to reduced HCP time for administration; 2) reduction in natalizumab-TYS exposure during pregnancy; 3) reduction in risk of PML; 4) reduction in travel and in-clinic time for patients and carers (drug administrations). The Company believes that the Final Guidance should reflect the value that EID for natalizumab-TYS IV and SC provides to the NHS and patients.	
4	The Company agrees with the Committee's preference for the EAG to explore EDSS-specific SMRs within the economic model, as reflected in our response to the EAG report and supported by clinical expert feedback from the first Committee meeting, relevant literature, and the Committee's preference in the recent appraisal of cladribine for treating relapsing multiple sclerosis (ID6263).[6–10] While acknowledging the limitations of Harding *et al*., as outlined in the NICE draft guidance for this appraisal, the Committee in the cladribine appraisal concluded that the SMRs in Harding *et al*. were the best available source of excess mortality in this population and aligned with the NHS population. Therefore, the Company considers that scenarios using EDSS-specific SMRs, at least partially informed by Harding *et al*., are more appropriate than the constant SMR from Jick *et al*. (2014),(3, 4) which informed the EAG base case.	The EAG have considered this feedback and followed an approach partly informed by Harding 2018 and partly by Jick 2014. (3, 4) Details are in Section 1.9 and Section 2.1.
5	The Company is also concerned at the potential equality issues raised by the draft guidance. Natalizumab is the only high-efficacy therapy that clinicians in England and Wales are able to give in pregnancy. Feedback from clinicians to the Company is that if a pregnant woman is not offered treatment, then this is a disadvantage and may lead to worse outcomes. For example, a case study in a pregnant woman where natalizumab-TYS was discontinued rapidly triggered a life-threatening case of immune reconstitution inflammatory syndrome (IRIS), which fully resolved on re-starting natalizumab-TYS later in pregnancy. The Company is therefore concerned at the potential for some patient groups, including pregnant women, to be disadvantaged by the current decision.	See section 1.3
6	The Company would welcome further dialogue with NICE and the EAG on further updates to the economic model and analyses as access to key underlying data in the decision making inputs is currently limited e.g. MS registry. Areas for discussion would include, but not be limited to:	See Section 1.10. The EAG, in collaboration with the MS Registry, have completed the

Comment number	Comments	EAG response
	• Additional information on the quality and relevance of the data from the MS Register, including completion of the DataSAT tool in NICE's real-world evidence framework for all potential data sources • The proportion of people with secondary-progressive MS in the model at 5, 10 and 15 years • Survival curves showing predicted survival in the model	DataSAT form and included in the appendix. The EAG have estimated proportions SPMS at 5, 10 and 15 years and generated survival curves.

Comments from ABN

#	Comments	EAG response
1	We read with disappointment the draft TA finding that natalizumab would not be recommended for use in the NHS in those with highly active MS. We feel that this recommendation does not take into account the substantial clinical value that being able to use natalizumab according to the current license would bring. There is a need for a non-immunosuppressive treatment option for people with MS failing first line treatment. Natalizumab is the only highly effective therapy for MS not associated with systemic immunosuppression. During the COVID-19 pandemic, natalizumab was temporarily available for people with highly active MS due to its mechanism of action (in contrast to other therapies associated with higher risk of severe COVID); this was highly valued by both patients and clinicians. Additionally, natalizumab can be started more rapidly than other highly effective treatments, without the need for prescreening and potential vaccination (varicella, mumps, pneumococcus etc). This is a hugely desirable quality where a treatment switch is needed urgently due to clinical deterioration. These recommendations are in contrast with clinical practice in other European countries, placing patients treated in England at significant disadvantage.	No EAG response needed.
2	We note that the cost analysis of natalizumab presented in the draft TA refers to 4-weekly dosing. Many centres are now using 6-weekly dosing for the majority of patients as part of PML risk mitigation and management of infusion suite capacity. With reduced treatment frequency, both drug and NHS infusion-associated costs reduce by c33%, in addition to potential reduction in costs associated with safety monitoring given risk mitigation. Subcutaneous administration, whilst predominantly given in hospital, saves staff hours through shorter administration times, whilst continuing to deliver this treatment in safe environment.	See sections 1.7 and 1.8
3	We additionally raise the following equalities scenarios which we believe have not been fully taken into account: Natalizumab treatment is safe during pregnancy, and its continuation is recommended during conception and pregnancy according to both UK and international guidance. Where patients on antiCD20s have breakthrough inflammatory disease, they currently have no pregnancy-compatible DMT to escalate to without waiting for a second clinical relapse. Men in this situation have the option of fingolimod (teratogenic) or alemtuzumab/cladribine (induction therapies with long washout). Women wishing to try to conceive should not take these therapies whilst trying to conceive. Lack of access based on not meeting the relapse criteria mean that women who are pregnant or trying to conceive are excluded from having access to appropriate treatment. A PPP based on this consideration was being prioritised for consideration by NHSE on an equalities basis prior to this MTA; this was suspended as a result of this MTA. Secondly, in older patients with MS where the risk of infections is particularly increased, natalizumab may offer a safer non immunosuppressive treatment option in the context of active disease.	See section 1.3
4	References 1. NHS England DMT algorithm https://www.england.nhs.uk/wp-content/uploads/2024/03/treatment-algorithm-for-multiple-sclerosis-disease-modifying-therapies-july-23.pdf 2. Smets et al 2022. https://pubmed.ncbi.nlm.nih.gov/34902761/ 3. Giovannoni et al 2021 https://pmc.ncbi.nlm.nih.gov/articles/PMC8286545/	

#	Comments	EAG response
	4. Dobson et al 2019. https://pubmed.ncbi.nlm.nih.gov/30612100/ 5. Fillipi et al 2024. https://pubmed.ncbi.nlm.nih.gov/37715789/	

Comments from the MS Society

#	Comments	EAG response
1	We are disappointed by the initial decision not to recommend natalizumab and its biosimilar for use in people with highly active relapsing remitting MS (RRMS) despite a full course of another disease modifying therapy (DMT). Recommending natalizumab for this group would increase patient choice for people with highly active RRMS. People in this group are already offered natalizumab in Wales, Scotland and Northern Ireland, so a recommendation would reduce geographical disparity in access to a high efficacy DMT in the UK. People with MS often face profound uncertainty(1), and we know that choosing a DMT is a highly personal decision requiring each individual to consider the risks and benefits – for them – of the different DMTs(2). The more effective treatments are available to wider populations, the greater the choice for patients. (1) Van Reenen et al. (2025) The liminal space between hope and grief: The phenomenon of uncertainty as experienced by people living with relapsing-remitting multiple sclerosis Available at: https://pmc.ncbi.nlm.nih.gov/articles/PMC11774396/ (2) Manzano, A. et al. (2019) CRIMSON - Considering Risk and benefits In Multiple Sclerosis treatment selection: Final Report	No EAG response needed
2	A decision not to recommend natalizumab may have a disproportionate impact on people of childbearing age, and particularly women, who are more likely to consider family planning and pregnancy in their treatment decisions. Pregnancy and maternity are protected characteristics. There is no evidence that natalizumab harms unborn children, and treatment is generally continued through pregnancy. Of the comparator DMTs for this appraisal, courses of ocrelizumab (subcutaneous and intravenous), ofatumumab and ublituximab are paused during pregnancy. Cladribine is the only comparator that someone can benefit from for the full duration of pregnancy, though restrictions remain as pregnancy should be delayed until 6 months after the year 2 dosage. Unlike natalizumab, cladribine is classified as having 'good efficacy'. This means that a decision to recommend natalizumab would make it the only high efficacy DMT available to this population without restrictions on family planning. This would address a currently unmet need and potential gendered inequality to high efficacy DMTs, reported elsewhere(1). As our patient expert puts it, 'empowering people living with MS to effectively treat their MS whilst also providing opportunities for them to fulfil other ambitions is critical. For women with MS who would like to grow their families and are	See section 1.3

#	Comments	EAG response
	planning pregnancies, there are very few choices for them to fulfil both these ambitions. Reflecting on my own experience as a young woman whose MS was highly active being faced with the potential choice of prioritising a more effective treatment or having a baby, it made a significant difference talking to my neurologist and the specialist pregnancy nurse who informed me that I didn't have to choose one or the other with the option of natalizumab. Managing physical and mental health is an important part of living well with MS and something I don't think should be underestimated.' (3) Vukusic, S., et al. (2024). Is there therapeutic inertia in women with MS? Presented at ECTRIMS 2024	

Comments from MS Trust

#	Comments	EAG response
1	We think that some commentators may be underestimating the prevalence of Advanced MS. Many people living with advanced and complex symptoms of MS will not be under the care of Neurology teams but will be cared for directly by General Practice and District Nursing, or alternatively in Palliative Care or residential care homes. Our research indicates that there could be as many as 40,000 people with Advanced MS in the UK, although this is hard to determine as they may not appear on Neurology caseloads and there are issues with coding patients in GP records. This means that the chances of a person with RRMS proceeding to advanced states of disability may be higher than the model suggests. The costs to the NHS of caring for people in advanced stages of MS, including hospital admissions for things like UTIs and falls needs to be considered.	The EAG recognises that the model does not cover the full complexity of advanced stages of MS. As with any modelling exercise, it is a simplification but attempts to cover the most important elements from a costs and effects perspective. The EAG similarly recognises that progression to advanced MS (i.e., SPMS in the model) is based on the MS Registry and that this carriers with it potential limitations, including the imperfect coding noted by the stakeholder.
2	We hear from people taking natalizumab and from health professionals (including at our annual Conference earlier in March 2025) that extended interval dosing is very common and widely accepted. This means that the real-world costs of natalizumab are less than indicated.	See section 1.7

#	Comments	EAG response
	This is also particularly relevant in the context of treating women with MS through conception, pregnancy and post-childbirth. There is a high chance of post-birth rebound activity in women with highly active MS, meaning that they are at risk of relapse if they stop controlling their MS during pregnancy. By utilising the extended interval dosing, they can time their infusions to avoid the third trimester, (which is the only point at which natalizumab may influence the baby) and restart in time to resume maternal protection.	
3	The recommendations as they stand represent a disappointing outcome for women with highly active MS planning pregnancy and this is **a significant equalities issue**. These women will now face devastating choices – to expose their foetus to a drug with known negative side-effects (all the relevant comparators), to not take any disease modifying drug and expose themselves to the risk of catastrophic and permanent disability at the point of becoming a mother to a newborn, or to not become a mother at all. This is very serious, and we feel strongly that natalizumab should be considered as an option for neurologists supporting women of childbearing potential with highly active RRMS. As women are up to three times more likely to get RRMS than men, this is a significant problem and will lead to harm for women and families.	See section 1.3
4	To people living with RRMS, the distinction into different forms or types is meaningless. These categorisations are somewhat recursive, based in part upon assessing how effective a previous treatment has been. If you've been lucky enough to select a drug that works first time, you might think your MS was relatively inactive, when it was simply a good match between your treatment and your personal physiology. Until we know why some people respond better to some disease modifying drugs than others, it makes no sense to restrict the ability of neurologists and patients to make a choice where lifestyle and other considerations With AI support of DMD prescription choices being developed (e.g. Personalised Treatments Group, Cambridge) coming in due course, not having this flexibility could further delay prescription accuracy, subject people to unwarranted side effects and less effective treatments, and cause higher spending than needed by the NHS.	No EAG response needed as relates to general clinical practice and choices by NICE in setting the topic.
5	We know there are situations where natalizumab is being given at home by a health professional, to the benefit of patients who are otherwise unable to travel. We think it is important to consider this option, as there are many reasons why patients with MS might be unable or unwilling to travel long distances, including comorbidities (very common in MS), disabling symptoms, and cost. We know patients who have chosen therapies based on the travel required, making this an equalities issue based on household income.	The EAG note that this is not captured by the modelling. The committee may consider this equalities issue.

Comments from Dr Ruth Dobson

#	Comments	EAG response
1	I was disappointed to read the negative TA, which was essentially based on a lack of direct comparative and cost data leading to challenges with the modelling. This decision leaves people with MS who have disease activity on highly effective first line	EAG believe that this is a complex but common issue.

#	Comments	EAG response
	therapy (antiCD20 or cladribine) without access to a highly effective treatment unless they wait for a second relapse. The result of this decision will be irreversible disability for some people living with MS.	Please see response to point below.
	I note that the committee concluded that natalizumab would be a welcome additional treatment option for people with highly active RRMS, but did not find it suitable on the basis of complex statistical models rather than the clinical and patient need. Natalizumab has a unique mechanism of action which is not immunosuppressive. For people who have breakthrough relapse following cladribine, this negative TA means that their only options are long term immunosuppression or HSCT. The ability to use natalizumab after a single breakthrough relapse would offer patients who have developed disease activity after such treatments a non-immunosuppressive option. To my mind, as a clinician, this is a decision based on the absence of ability of statistical models to capture real world complexity and patient need.	EAG agree that the models and evidence are limited. However, it is not possible to say if more sophisticated modelling or additional evidence would lead to a more or less favourable view of natalizumab in HARRMS. It is therefore necessary to make a decision based on the current evidence while acknowledging the limitations.
	The recent TA recommending the availability of cladribine for people with active MS requiring high efficacy treatment leaves natalizumab as the only product requiring 2 relapses on treatment for escalation. There is an equalities issue here for those who relapse on antiCD20 therapies; as pregnancy is contraindicated within 6 months of taking cladribine treatment, those who relapse on antiCD20 therapies and wish to get pregnant within 18 months will have no available effective treatment with a safety record in pregnancy to use. Given that cladribine has similar wash out periods for males and females, and that the population seeking more rapid pregnancy are likely to be older this decision discriminates on the basis of age and pregnancy.	See section 1.3

Comments from Dr Sharon Letissier

#	Comments	EAG response
1	No acknowledgement for time of infusions and consumsables that are used	See section 1.8
2	As knowledge regarding MS and relapses have expanded. It is regarded that treating MS aggressive will/may slow brain atrophy. This essential in long term management of MS and consequently ensuring people with MS can stay at work and they may access Health care re Hospital/GP services thus sagving money and resources	No EAG response needed
3	**Marketing authorisation indication, section 2.1 -** These statement are not consistent with other High efficacy treatments. re CD 19 drugs have potential for long term Cd 20 suppression	No EAG response needed
4	**Price, 2.4 -** for S/C- comes in prefilled syringes so no consumables are required. in hospital less time, so more patients can be treated than IV tyruko and IV OCrevus. therefore less wait time for treatment	See section 1.8
5	Price, 2.5 - this is the cost price - IV Tyruko- longer stay in hospital 1hour, need cannula, saline flush, giving set and pump. no cost in the document for the consumable that are need by the trust administering the IV. there are hidden costs that have not been taken into consideration	See section 1.8
6	Section 3.1, 'the patient expert explained that many people feel a loss of independence when diagnosed with an incurable condition such as MS. As the condition progresses, people become increasingly disabled, which can worsen their quality of life and that of their carers. The committee concluded that RRMS can have a substantial impact on quality of life.' Therefore treating patients earlier will benefit the above and keep people at work and less time of work	No EAG response needed
7	Treatment waning, section 3.13. Need more real world data.	See section 1.5
8	Subsequent treatments in the model, section 3.14, 'The EAG highlighted that 35% of people in the model had third-line treatment (that is, 1 additional subsequent treatment) and 34% of people had fourth-line treatment (a second subsequent treatment) over the modelled lifetime.' if treat adequately at first will prevent swapping DMTs and this wastage that occurs	EAG agree that if initial treatment is successful fewer patients will required 3rd or higher treatment.
9	Subsequent treatments in the model, section 3.14, 'People who developed secondary-progressive MS were assumed to have a basket of siponimod or interferon beta 1b as a weighted average by use in the MS Register' not all patients can recieve Siponimod re criteria, genotype testing and contraindications	EAG agree. However, the individual treatments and eligibility are not modelled. For simplicity an average of SPMS treatment, as represented by outcomes of patients recorded in the MS registry, is used. This reflects clinical practice so includes patients who do not receive Siponimod due to containdications.

#	Comments	EAG response
10	Natalizumab dosing regimen, section 3.17 - no consumables have been acknowledged in the costing and more time taken infusion chair	See section 1.8
11	Natalizumab administration routes, section 3.20, 'the company that makes natalizumab originator said that subcutaneous natalizumab was associated with reduced administration time and so reduced treatment burden and NHS costs.' We see this in practice	See section 1.8
12	Equality, section 3.25. This can be used in pregnancy and it is acknowledge post partum there may be a risk of more relapses and can breast feed on Tysabri.	See section 1.3

Appendix: DataSAT form related to MS Registry analyses

Research question

The research question is what real-world treatment sequences do people with highly active relapsing remitting multiple sclerosis (HARRMS) receive in the UK and what are their outcomes on available treatments. We will answer this question using data from the UK MS Register. This supports economic modelling. We specifically estimate proportions of individuals transitioning from second-line to third-line disease-modifying therapies (DMTs), proportions on second-line and third-line DMTs, rates of EDSS increase, rates of EDSS decrease, rates of relapse, and rates of progression to SPMS. We estimate these in both HARRMS who have received at least one previous DTM and in any RRMS.

Data provenance

Please see recommendations for reporting data provenance.

Item	Response
Data sources	UK MS Register (UKMSR), self-reported data extracted August 2024.
Data linkage and data pooling	No external datasets were linked for this analysis. All analyses based on data collected within the UKMSR.
Type of data source	Longitudinal patient-reported outcome data.
Purpose of data collection	The UKMSR is a research based disease registry linking clinical and self-reported outcomes to help improve understanding MS disease progression, treatment outcomes, and general quality of life for people with MS.
Data collection	• Treatment data: DMT types, treatment dates • MS Phenotype and progression dates • Relapse dates and severity • EDSS (Leddy S, Hadavi S, McCarren A, Giovannoni G, Dobson R. Validating a novel web-based method to capture disease progression outcomes in multiple sclerosis. J Neurol. 2013 Oct;260(10):2505-10. doi: 10.1007/s00415-013-7004-1. Epub 2013 Jun 27. PMID: 23807152.)
Care setting	Direct patient reporting via our secure online portal and NHS Neurology clinics
Geographical setting	The UKMSR is proportionally represented by participants from all of the constituent countries of the United Kingdom
Population coverage	The UKMSR has >25,000 participants with MS which covers a broad population with some selection bias due to being an online registry, however efforts to diversify the cohort via active recruitment on the lifespan of the registry has led to more proportional representation.
Time period of data	Data collection has been ongoing since April 2011.

Data preparation	Data was extracted using the R version 4.4.0 programming language with the DBI and ODBC packages, pre-processed using the tidyverse packages, and EQ5D scores processed using the eq5d package. The instruments that were used by the UK MS Register were pre-processed as follows: Participants – Register users had to contain the following info to be considered: • MS at Diagnosis recorded as either RRMS or SPMS • Current MS Type recorded as either RRMS or SPMS • Year of birth must be present • Gender must be provided and either Male or Female. Those who recorded “Prefer not to say” on Gender were excluded due to low counts. • Age at time of study (2024) had to be between 18-100 • Date of Current MS Type must be recorded and valid (i.e after onset/diagnosis dates, after year of birth). • Have at least 1 DMT recorded in their medications • Have at least 2 webEDSS readings. For dates of MS Onset, Diagnosis, and Current MS, users can indicate that they do not know the month/year of the date in question. In cases where the month is unknown, the month is inferred to be January. WebEDSS – In the event that users made multiple webEDSS submissions on the same day, the latest webEDSS entry made on that day was used, with other entries discarded. Self-Reported Medications – Medications were grouped into main DMT components, and on initial filtering, any entries which: • Were flagged as having started after August 15th, 2024 • Started after the date the medication entry was filled in on the register website • Had a zero day duration (Start date being equal to end date) were excluded and filtered out of the medications. In the event that multiple DMTs were logged with no stop date with the potential to cause a clash with another DMT, a timeline was constructed where a stop date was inferred based on the next DMT’s start date minus 1 day to ensure that only DMT was in use at a time. Relapses – Users on the register can indicate if they had any relapses in the last 6 months and to identify the month of the most recent relapse. Pre-processing was performed on these responses to check that the month reported on the relapse corresponds to being within 6 months of the completion of the relapse survey. EQ5D – EQ5D-5L responses were gathered to link to the latest webEDSS readings from users. To calculate the index score from the EQ5D components, the 5L UK Crosswalk algorithm was used in the eq5d package (https://www.sciencedirect.com/science/article/pii/S1098301512000587).

Data governance	The UK MS Register is managed and maintained by Swansea University Medical School and is primarily funded by the MS Society. The UKMS Register has ethical approval from South West Central Research Ethics Service 21/SW/0085 It operates under strict governance protocols where data is made pseudonymously available to accredited researchers after suitable review. The platform has high security standards being ISO 27001 accredited with regular external security audits with annual penetration testing. The system benefits for extensive network segmentation and data protection backups. For researchers to access these data there is a formal process where an expression of interest leads to a feasibility meeting with register team. This then moves on to a formal collaboration request which is then assessed by the governance review board. If the project is approved then data assess agreements are signed and relevant training is assign. Only then are the data provisioned. The register is fully compliant with GDPR/Data Protection Act 2018
Data specification	A data dictionary sufficient to data provided for each project is provided as needed.

Data management plan and quality assurance methods	The Secure eResearch Platform (UKSeRP), has achieved ISO27001 accreditation, as a consequence of the audit level required to attain this. All host systems servers and software, electronic and physical security are maintained to these standards. To that end we use the term UKSeRP below This network covers the data networks, LAN-attached servers and personal computers (stand-alone or network- enabled), located at company offices and company production related locations, where these systems are the responsibility of UKSeRP, and any personal computers, laptops, mobile device and or servers authorised to access the company's data networks. Data are backed up to a schedule as agreed with the UKSeRP tenant. Typically this takes the form of daily entire system backups and hourly transaction log shipping from databases. All backups are fully documented – covering configuration and usage instructions. All backups are stored securely onsite within UKSeRP access-controlled areas / secure perimeter (but remote from backup infrastructure location) on the main Swansea University campus. Access to data stored in SeRPs is approved by an information governance committee who will review project access. This is typically made up of a team member, several people affected by the conditions, academics from outside of Swansea University and clinicians from the NHS. Access to anonymised data is then granted and users must sign a data sharing agreement, similar to this one: https://redcap.ukmsregister.org/surveys/?s=8HRC4KLCW9 They must also complete a GDPR course from a recognised provider and present this and a CV to the research team. Data are provided to researchers via the SeRP. Comprising the security and governance layer then 2 factor remote access to anonymised data via SPSS/R/SAS/Stata as appropriate. Line level data are not allowed out and all requests for data are reviewed by a senior analyst. Data are retained for the duration of the research unless participants elect to leave the study. In this case all identifiable data are purged although the research data will remain. This is due to publications/analyses potentially having been based on these data. The terms for this are clear to participants should they choose to leave the study. Typically, most data is kept for 21 to 25 years or for the duration of the study should it be longer. Data reside in databases as laid out in the data dictionaries for the project. Where it is linked to other data sources – Such as SAIL documentation for that are kept. All accesses, user rights, requests for data out and ultimately publications will be logged by the system.

Other documents	https://ukmsregister.org/Research/OurData 1. Nicholas, R. et al. The impact of healthcare systems on the clinical diagnosis and disease-modifying treatment usage in relapse-onset multiple sclerosis: a real-world perspective in five registries across Europe. Ther Adv Neurol Disord 16, 17562864231198963 (2023). 2. Middleton RM, Rodgers WJ, Chataway J, *et al.* Validating the portal population of the United Kingdom Multiple Sclerosis Register. *Multiple Sclerosis and Related Disorders* 2018;**24**:3–10. doi:10.1016/j.msard.2018.05.015 3. Osborne LA, Middleton RM, Jones KH, *et al.* Desirability and Expectations of the UK MS Register: Views of People with MS. *International Journal of Medical Informatics* 2013;**82**:1104–10. doi:10.1016/j.ijmedinf.2013.07.005 4. Ford DV, Jones KH, Middleton RM, *et al.* The Feasibility of Collecting Information from People with Multiple Sclerosis for the UK MS Register via a Web Portal: Characterising a Cohort of People with MS. *BMC Medical Informatics and Decision Making* 2012;**12**:73. doi:10.1186/1472-6947-12-73 5. Kuri A, Dobson R, et al. Evaluation of remote assessments for multiple sclerosis in an in-home setting. *Multiple Sclerosis and Related Disorders* 2021;**54**. doi:10.1016/j.msard.2021.103125

Data quality

Details of data quality should be provided for key study variables including population eligibility criteria, outcomes, interventions or exposures, and covariates.

Study variable	Target concept	Operational definition	Quality dimension	How assessed	Assessment result
What type of variable (for example, population eligibility, outcome)	Define the target concept (for example, myocardial infarction [MI])	Define operational definition. For example, MI defined by an ICD-10 code of I21 in the primary diagnosis position	Choose: accuracy or completeness	Describe how quality was assessed. Provide reference to previous validation studies if applicable.	Provide quantitative assessment of quality if available. For example, 'positive predictive value 85% (75% to 95%)'
MS Type at diagnosis	Diagnosis		completeness		100%
MS Type Now	Diagnosis		completeness		100%
Self-reported medication	Drug		completeness	Selected self-reported disease modifying therapies (DMTs) of interest	At least 1 per patient
Web EDSS	PRO assessment		completeness		At least 2 per patient
Self-reported Relapse	PRO assessment		completeness	Users report any relapses as they occur. If none reported then assumption that no relapse occurred	
EQ5D	PRO assessment		Completeness	QuoL Index linked to webEDSS	

These data supported treatment analysis on RRMS and Highly active RRMS (defined as having more than 1 DMT and an EDSS score >= baseline score). Relapse and Disease type where used to access relapses and progression to SP.

Data relevance

Please see recommendations for reporting data relevance.

Item	Response
Population	The UKMSR population is representative of the population of people with MS being treated at NHS neurology clinics (Middleton, et al. 2018). Self-reported treatments have been validated using linked data from partner NHS treatment centres where the patient has consented to do so.
Care setting	See above, our population and treatment pathways are representative of NHS treatment protocols at UK neurology centres.
Treatment pathway	See above, all participants in the UKMSR have a confirmed diagnosis of MS. All treatments over the course of the disease are self-reported via our online secure portal.
Availability of key study elements	See data preparation section. Data selected such that each participant had a valid entry for MS type at diagnosis and current MS Type, Date of birth, Sex, have record of at least one DMT and at least 2 EDSS scores.
Study period	The study period ranged from first EDSS visit of 03/01/2015 and last recorded EDSS visit 13/08/2024, DMTs could be any treatment available on the NHS during this time period.
Timing of measurements	All measures were self-reported and generally recorded after the fact. For example each questionnaire window is every 6 months and we ask if there were any relapses in the last 6 months, number and severity of latest. Date of SPMS progression is recorded after a diagnosis from a clinician so it can range from being recorded on the same day to many years after the fact. EDSS is recorded when the participant does the online assessment.
Follow up	Note how the follow-up period available in the dataset is sufficient for assessing the outcomes. The median number of EDSS assessments for this cohort were 5 and the mean follow up time was 3.84 years.
Sample size	2140 participants in the UKMSR met all the inclusion criteria described above.

References

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6. NHS England. 2021/22 National Cost Collection Data Publication 2024 [Available from: https://www.england.nhs.uk/publication/2021-22-national-cost-collection-data-publication/.
7. National Institute for Health Care Excellence (NICE). [TA127] Natalizumab for the treatment of adults with highly active relapsing–remitting multiple sclerosis 2007 [Available from: https://www.nice.org.uk/guidance/ta127.

EAG responses to NICE queries, 20th May 2025.

- **EAG to check where the discontinuation rates due to AE come from (slide 15).** The baseline discontinuation rate used is from AFFRIM (Natalizumab IV300) because we model baseline event rates to follow patients on Natalizumab (this data obtained from the MS registry). Relative treatment effects are applied from the NMA (relative to natalizumab originator) to baseline event rates. Equal efficacy is assumed for Natalizumab originator and Natalizumab biosimilar on all the outcomes : CDP, ARR, SAEs, and discontinuation.
- **EAG to look at Biogen cost code used for natalizumab SC.**, AA30F. (£513) Medical care of patients with multiple sclerosis, with CC score 0-1. Day case. Ours is same one AA30F. Slightly higher (£626.13), our guess is it because we used an updated one in comparison to the company's.
- **EAG to look at explanation for higher administration costs in EAG model than in Sandoz cost comparison.** Cost comparison model was revised to be more similar to EAG's costs, but not the same. Sandoz assume administration costs are accounted for with the use of HRG4+ day case costs and similar number of visits is assumed to EAG's frequency of visits. The EAG assumes a higher cost for the day case (£626.13), and one additional annual monitoring visit for patents to undergo routine surveillance, bloods, MRI, etc.. The cost comparison model does not assume time saving related to the SC formulations.

Additional analyses post ACM2

ID6369: Natalizumab and Tyruko (natalizumab biosimilar) for treating highly active relapsing-remitting multiple sclerosis after at least one disease modifying therapy: a systematic review and economic model

Produced by: Bristol Technology Assessment Group, University of Bristol

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Additional Analyses requested

Analysis	Description
Scenario 11. Sensitivity assuming realistic progression onto SPMS	Limits progression of patients on to SPMS to those with an EDSS score > 4.5 as per clinical opinion of some committee members
Scenario 12. Sensitivity assuming realistic progression onto SPMS + assuming a reduction in Natalizumab-SC administration costs.	Reduces administration cost by a factor of 0.5x for Natalizumab-SC year 1 onwards to explore the company's assumption of reduced resource use (nurse administration hours per year). No further cost reduction associated with the company funded home administration.

TABLE 1 INCREMENTAL NET BENEFITS RELATIVE TO NATALIZUMAB-IV AT £20,000/QALY FOR SCENARIOS 11 AND 12 (PUBLICLY AVAILABLE LIST PRICES)

Treatment	Scenario 11	Scenario 12
Natalizumab-SC	-341.62 (-30,440.38, 28,115.85)	31,631.89 (2,086.52, 65,503.56)
Natalizumab biosimilar-IV	12,731.58 (-20,276.80, 42,088.66)	12,794.11 (-18,688.43, 42,183.58)
Cladribine	98,955.05 (44,776.28, 159,321.60)	98,938.85 (44,476.63, 159,090.90)
Ublituximab	-26,254.14 (-55,680.78, 2,863.66)	-26,439.05 (-56,148.11, 2,730.27)
Ofatumumab	-28,063.67 (-53,711.86, -596.95)	-28,099.33 (-54,613.77, -1,173.19)
Ocrelizumab	-46,974.91 (-77,905.37, -18,468.97)	-47,087.23 (-78,228.86, -17,962.25)

TABLE 2 INCREMENTAL NET BENEFITS RELATIVE TO NATALIZUMAB-IV AT £30,000/QALY FOR SCENARIOS 11 AND 12 (PUBLICLY AVAILABLE LIST PRICES)

Treatment	Scenario 11	Scenario 12
Natalizumab-SC	-1,664.20 (-38,122.94, 39,541.15)	30,309.32 (-4,963.83, 69,933.75)
Natalizumab biosimilar-IV	12,797.68 (-29,002.73, 43,810.51)	12,860.21 (-28,683.06, 43,346.42)
Cladribine	96,131.76 (34,825.31, 167,103.25)	96,115.56 (34,525.66, 167,488.38)
Ublituximab	-27,916.35 (-62,517.70, 4,557.65)	-28,101.25 (-63,608.69, 4,612.08)
Ofatumumab	-31,934.80 (-68,686.93, 5,013.74)	-31,970.47 (-68,156.95, 5,219.17)
Ocrelizumab	-48,523.83 (-87,956.43, -14,945.56)	-48,636.15 (-87,647.09, -14,680.06)

MODEL VALIDATION OUTPUT:

- The proportion of patients on natalizumab after 10 years:
  - 88% of those who started on Natalizumab.
  - 45% of those who started on any treatment .
- Average starting age 36 years.
- Average age at death 77 years.
- 33% progressed to SPMS.
- 67% received a subsequent treatment line:
  - 35% of patients receive 2nd and 3rd line treatments.
  - 32% of patients receive 2nd , 3rd and 4th line treatments.

TABLE 3 PROPORTION OF PATIENTS PROGRESSING ON TO SPMS AT 5, 10 AND 15 YEARS FOR SCENARIO 11, LIMITING THE PROGRESSION TO PATIENTS WITH EDSS > 4.5

Treatment	5 years	10 years	15 years
Natalizumab-IV	9.13%	13.10%	15.04%
Natalizumab-SC	8.64%	12.31%	14.09%
Natalizumab biosimilar-IV	9.31%	12.91%	14.28%
Cladribine	9.45%	12.98%	14.81%
Ublituximab	8.96%	12.91%	14.69%
Ofatumumab	9.51%	13.36%	14.90%
Ocrelizumab	8.68%	12.96%	14.79%

TABLE 4 MODEL VALIDATION KEY OUTPUT FOR SCENARIO 11, LIMITING THE PROGRESSION TO PATIENTS WITH EDSS > 4.5

	Natalizumab IV	Natalizumab SC	Natalizumab biosimilar	Average of all treatments
Average time to event (years)				
Progression	9.765	9.782	9.765	9.764
Relapse	10.438	10.435	10.415	10.428
Average time spent on treatment (years)				
2nd line	9.995	10.007	9.983	9.970
3rd line	2.745	2.731	2.730	2.723
4th line	1.037	1.048	1.034	1.037
Average time spent in severity states (years)				
EDSS 0	1.491	1.488	1.489	1.466
EDSS 1	2.756	2.763	2.749	2.687
EDSS 2	5.292	5.299	5.284	5.225
EDSS 3	6.828	6.806	6.798	6.749
EDSS 4	7.710	7.692	7.695	7.701
EDSS 5	6.871	6.860	6.848	6.902

EDSS 6	5.013	5.021	5.020	5.074
EDSS 7	0.198	0.198	0.199	0.203
EDSS 8	0.004	0.004	0.004	0.004
EDSS 9	0.000	0.000	0.000	0.000