**National Institute for Health and Care Excellence**

**Single Technology Appraisal (STA)**

**Ozanimod for treating relapsing–remitting multiple sclerosis [ID1294]**

**Response to consultee and commentator comments on the draft remit and draft scope**

**Please note:** Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

**Comment 1: the draft remit**

| Section | Consultee/ Commentator | Comments [sic] | Action |
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| Appropriateness | ABN endorsed by RCP | Yes | Comment noted. No action required. |
| | Celgene Ltd | This is an appropriate topic for NICE to consider. | Comment noted. No action required. |
| | Merck | The topic is appropriate. | Comment noted. No action required. |
| | MS Society | Yes, ozanimod has shown promising results for treating relapsing MS in clinical trials, reducing the number of relapses compared to beta interferon. It also reduced the number of MRI lesions and slowed the loss of brain volume compared with beta interferon.<br>However, ozanimod has yet to be granted a marketing authorisation by the EMA so the appraisal timeline needs to fit with the EMA's licensing schedule. | Comments noted. NICE aims to provide draft guidance to the NHS within 6 months from the date when the marketing authorisation for a technology is |

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| | | | granted. No action required. |
| | Multiple Sclerosis Trust | Ozanimod has successfully completed phase III trials and the manufacturer now plans to file for marketing authorisation. It should therefore be referred to NICE for appraisal. | Comment noted. NICE aims to provide draft guidance to the NHS within 6 months from the date when the marketing authorisation for a technology is granted. No action required. |
| | Teva UK Limited | No comments | Comment noted. No action required. |
| Wording | ABN | Yes | Comment noted. No action required. |
| | Celgene Ltd | The population of interest is [redacted] | Comment noted. No action required. |
| | Merck | The wording is appropriate. | Comment noted. No action required. |
| | MS Society | Yes | Comment noted. No action required. |
| | Multiple Sclerosis Trust | Yes | Comment noted. No action required. |

| Section | Consultee/ Commentator | Comments [sic] | Action |
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| | Teva UK Limited | No comments | Comment noted. No action required. |
| Timing Issues | ABN | Routine | Comment noted. No action required. |
| | Celgene Ltd | Celgene would like to draw NICE's attention to the timelines below regarding the product licencing and marketing authorisation. | Comment noted. No action required. |
| | Merck | The topic is important | Comment noted. No action required. |
| | MS Society | We welcome NICE's timely consideration of ozanimod and urge them to conduct the appraisal as soon as possible in light of the EMA's decision on whether to grant ocrelizumab marketing authorisation. | Comment noted. NICE aims to provide draft guidance to the NHS within 6 months from the date when the marketing authorisation for a technology is granted. No action required. |
| | Multiple Sclerosis Trust | Ozanimod has not yet been submittted to European drug regulators for marketing authorisation. The treatment landscape for relapsing MS is in a state of flux at the present, with a number of comparators subject to ongoing NICE appraisals (beta interferons plus glatiramer acetate and ocrelizumab). We would recommend that NICE delays drawing up this Final Scope until ozanimod is further advanced in the licensing process and the outcome of the on-going appraisals is clearer. | Comments noted. NICE aims to provide draft guidance to the NHS within 6 months from the date when the marketing authorisation for a technology is |

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| | | | granted. No action required. |
| | Teva UK Limited | No comments | Comment noted. No action required. |
| Additional comments on the draft remit | Teva UK Limited | No additional comments | Comment noted. No action required. |

**Comment 2: the draft scope**

| Section | Consultee/ Commentator | Comments [sic] | Action |
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| Background information | ABN | Accurate | Comment noted. No action required. |
| | Celgene Ltd | No comments | Comment noted. No action required. |
| | Merck | The background information is accurate although the description of the review of TA32 will soon require updating (likely within the timeframe for finalisation of this scope). | Comments noted. The background section has been updated. |
| | MS Society | While the description for fingolimod describes the NICE recommendation, in practice fingolimod is also used for people who have relapses despite being treated with teriflunomide and dimethyl fumarate. It is also an alternative option for natalizumab patients at high risk of PML. | Comments noted. Thebackground section is intended to provide a brief overview of the disease and its management. |

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| | | The importance of early treatment for MS should be emphasised as the recognised medical consensus is that the earlier treatment is administered the better the outcomes will be for the person diagnosed with MS. This should be reflected in the background information as it is important that people with MS should be able to choose their first line of treatment when consulting with a neurologist. Please see the following links for more information:<br>MS Society website for further details<br>http://www.mssociety.org.uk/earlytreatment<br>The Association of British Neurologist's most recent guidelines<br>http://pn.bmj.com/content/early/2015/06/20/practneurol-2015-001139.full<br>The MS Brain Health initiative<br>http://www.msbrainhealth.org/ | |
| | Multiple Sclerosis Trust | The background information states that the relapsing form of MS is characterised by periods of remission when symptoms are mild or disappear altogether. It is certainly not true that symptoms are mild or disappear altogether during periods of remission – in remission, people continue to experience the full range of symptoms such as fatigue, pain and cognitive impairment. Most people with MS experience one or more symptoms continuously, but between relapses this background level will remain more or less stable.<br><br>Background information does not capture the impact of MS on work and family life. People with MS are commonly diagnosed between the ages of 20 and 40 and may live with MS for 30-40 years. The variable nature of MS means that people given a diagnosis of MS and their families face many years of uncertainty. The disease can have a significant impact on work and family life, both for the individual and for informal carers. | Comments noted. The background section has been updated to reflect your comments. This section is intended to provide a brief overview of the disease and its management. |

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| | | Background information does not capture the importance of early initiation of disease modifying treatment. There is a considerable body of evidence and medical consensus that starting treatment as soon as possible after diagnosis leads to better outcomes. | |
| | Teva UK Limited | No comments | Comment noted. No action required. |
| The technology/ intervention | ABN | Accurate | Comment noted. No action required. |
| | Celgene Ltd | Requested revisions (denoted in bold below) to the 2 paragraphs describing ozanimod:<br>Ozanimod **down-regulates S1PR1 resulting in a decrease in** ~~decreasing~~ the number of circulating B and T lymphocytes.[1] Recovery of lymphocyte counts to the normal range have been reported within 2–3 days of drug cessation.[2] **It has shown therapeutic benefit in 2 clinical trials** compared to interferon beta-1a **~~and placebo~~** in adults with relapsing multiple sclerosis. Animal model studies have suggested it may be potentially neuroprotective through direct CNS effects, mediated in part by its direct activity on astrocytes.[1]<br>1. Taylor Meadows, K et al., P1183 ECTRIMS 2017.<br>2. Tran JO et al, Clin Pharmacol Drug Dev. 2017 Aug 7<br>~~It may have the potential to prevent neurological damage by activating specific cells in the central nervous system.~~ Ozanimod is administered orally. | Comments noted. The intervention section has been amended to reflect the feedback. However, placebo has been retained because RADIANCE compared ozanimod with placebo. The evidence on the clinical benefit of ozanimod will be fully discussed by the appraisal committee. |

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| | Merck | No comments. | Comment noted. No action required. |
| | MS Society | Yes | Comment noted. No action required. |
| | Multiple Sclerosis Trust | Yes, we believe so. | Comment noted. No action required. |
| | Teva UK Limited | No comments | Comment noted. No action required. |
| Population | ABN | Appropriately defined | Comment noted. No action required. |
| | Celgene Ltd | As per recent NICE Technology Appraisals in multiple sclerosis (e.g. TA493, TA441), there are several subpopulations of the relapsing multiple sclerosis (RMS) population which should be considered during decision making. These subpopulations are described in the 'Comparators' section below. | Comment noted. No action required. |
| | Merck | No comments. | Comment noted. No action required. |
| | MS Society | There are also a number of people with primary progressive MS who have disease activity, evidenced by relapses that are not mentioned when further unpacking relapsing MS in the comparator section. | Comment noted. The subgroups included in the scope in the comparator section describe relapsing forms of multiple sclerosis and therefore excludes primary |

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| | | | progressive multiple sclerosis which is characterised by gradual worsening of symptoms, rather than relapses. No action required. |
| | Multiple Sclerosis Trust | Yes, the population is defined correctly, subject to market authorisation. | Comment noted. No action required. |
| | Teva UK Limited | No comments | Comment noted. No action required. |
| Comparators | ABN | Yes, no single 'best alternative care' | Comment noted. No action required. |
| | Celgene Ltd | The subpopulations included within the draft scope are not consistent with recent NICE Technology Appraisals for relapsing multiple sclerosis (e.g. TA493, TA441).<br>Celgene suggests that the final scope includes the following subpopulations and comparators to reflect established NHS practice and ensure consistency with previous NICE Technology Appraisals:<br>• **For people who have not had previous treatment** (active [non-highly active non-RES] RRMS)<br>○ **Beta-interferon* [subject to ongoing appraisal]**<br>○ **Dimethyl fumarate**<br>○ **Teriflunomide** | Comments noted. The subgroups and relevant comparators have been updated.<br>Daclizumab has been removed from the list of comparators because its marketing authorisation has been withdrawn. |

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| | | • **For people who have received previous treatment** (active [non-highly active non-RES] RRMS)<br>  ○ **Dimethyl fumarate**<br>  ○ **Teriflunomide**<br>• **For people with rapidly-evolving severe relapsing-remitting multiple sclerosis**<br>  ○ **Alemtuzumab**<br>  ○ **Cladribine**<br>  ○ **Natalizumab**<br>• **For people with highly active relapsing-remitting multiple sclerosis despite previous treatment**<br>  ○ **Alemtuzumab**<br>  ○ **Fingolimod**<br>  ○ **Cladribine**<br><br>This is reflective of treatment practice and the 2015 Association of British Neurologists (ABN) Guideline (Association of British Neurologists: revised (2015) guidelines for prescribing disease-modifying treatments in multiple sclerosis; BMJ).<br><br>*To note, Extavia is the only NICE recommended treatment option of the beta-interferons and glatiramer acetate (interferon beta, glatiramer acetate (review TA32) [ID809]; Appraisal Consultation 1 Document). Clarity is therefore sought as to whether this is the only beta-interferon relevant to the Final Scope.<br><br>Further, as per NICE TA441: | |

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| | | The European Medicines Agency (EMA) has now restricted the use of daclizumab to patients whose disease has responded inadequately to at least 2 disease modifying therapies (DMTs) and cannot be treated with any other DMTs (see the EMA website for further details). This means that part of the population in whom daclizumab is currently recommended in NICE technology appraisal guidance 441 is outside the revised licensed indication of the drug. NICE is currently considering the appropriate next steps for NICE technology appraisal guidance 441.<br>Thus, the group 'people with relapsing-remitting multiple sclerosis' currently listed in the draft scope nor the above proposed subpopulations are representative of people eligible for treatment with daclizumab. It is therefore recommended that daclizumab be removed as a comparator from the Final Scope of this appraisal.<br><br>Additionally, Cladribine is not recommended by NICE as a treatment option in either of the above proposed subpopulations, nor the group of 'people with relapsing-remitting multiple sclerosis' currently in the draft scope. As per Guidance from TA493, Cladribine is recommended in:<br>• rapidly evolving severe relapsing–remitting multiple sclerosis, that is, at least 2 relapses in the previous year and at least 1 T1 gadolinium-enhancing lesion at baseline MRI or<br>• relapsing–remitting multiple sclerosis that has responded inadequately to treatment with disease-modifying therapy, defined as 1 relapse in the previous year and MRI evidence of disease activity.<br>This latter subpopulation aligns with the currently scoped subpopulation of:<br>• For people with highly active relapsing-remitting multiple sclerosis despite previous treatment.<br>This subpopulation is often referred to as 'suboptimally treated relapsing-remitting multiple sclerosis'. Currently, Cladribine is omitted from this | |

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| | | subpopulation in the draft scope, which is not aligned to the NICE recommendation in TA493.<br><br>Celgene recommends that ocrelizumab is removed as a comparator from all subpopulations included in the scope. Since final NICE guidance is not available for ocrelizumab, it is an inappropriate comparator for decision making as it does not form part of established NHS practice at this time.<br><br>Celgene recommends that the clinical definitions for each subpopulation are defined with the Final scope.<br><br>Celgene considers that alemtuzumab should be included as a relevant comparator within the following subpopulations only to reflect established NHS practice:<br>• rapidly evolving severe relapsing MS (no previous treatment)<br>• highly active RRMS despite previous treatment<br>The ABN have recommended use of alemtuzumab is only justifiable when there is clinical evidence of high-disease activity despite treatment (Scolding N et al., et al. Pract Neurol 2015;0:1–7.), due to its more complex safety profile, in line with natalizumab. The ABN expert group also noted that only in rare cases should there be escalation with rapid MRI lesion acquisition in the absence of clinical relapses. The clinical spirit of this positioning in a "highly active-like" subpopulation is reflected in a more explicit DMT algorithm which is in current development by the ABN and has been shared recently with the MS community (http://multiple-sclerosis-research.blogspot.com/2018/02/how-easy-is-it-to-design-algorithm-to.html#more). Another more recent EU expert guidance publication (Berger T el., CNS Drugs. 2017 Jan;31(1):33-50) has echoed the ABN guidance, | |

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| | | recommending that alemtuzumab is predominantly used in non-responders to previous treatment, with only a comparative minority in first line, treatment naïve patients with rapidly evolving MS (or a clinical relapse accompanied by an increase in the number of T2 lesions and/or ongoing evidence of Gd? T1 lesions).<br>  <br>Given the indication Celgene is seeking, it is suggested that the group 'For people with secondary progressive multiple sclerosis with active disease, evidenced by relapses' is removed from the scope of this proposed appraisal. | |
| | Merck | Cladribine tablets are recommended as an option for treating highly active multiple sclerosis in adults, only if the person has:<br>•rapidly evolving severe relapsing–remitting multiple sclerosis, that is, at least 2 relapses in the previous year and at least 1 T1 gadolinium-enhancing lesion at baseline MRI or<br>•relapsing–remitting multiple sclerosis that has responded inadequately to treatment with disease-modifying therapy, defined as 1 relapse in the previous year and MRI evidence of disease activity.<br>As such, Merck would expect to see cladribine tablets additionally listed as a comparator for 'people with highly active relapsing-remitting multiple sclerosis despite previous treatment'. | Comments noted. Cladribine has been added to the subgroups of patients with rapidly evolving and highly active relapsing-remitting multiple sclerosis. |
| | MS Society | The terminology used to describe the subgroups of MS for different treatment eligibility is getting unnecessarily complicated. For example 'highly active' and 'rapidly evolving severe' essentially describe the same thing, but | Comments noted. The subgroups and relevant |

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| | | are being applied to slightly different scenarios. It is clear that this is resulting in confusion as there are several errors within the outlined categories. This includes:<br><br>- In 'relapsing-remitting multiple sclerosis' fingolimod should be included as a 2nd line treatment.<br>- In 'people with rapidly evolving severe relapsing remitting MS' daclizumab is mentioned as a 3rd line option. For consistency, fingolimod should be included as a 2nd line option.<br>- In 'highly active relapsing remitting MS despite previous treatment' cladribine should be included.<br>- In 'people with secondary progressive MS with active disease, evidenced by relapses' Betaferon should be included.<br><br>It would be helpful for NICE to simplify its terminology and move away from unnecessary distinctions which stem from the slightly different wording of the various NICE STA recommendations. This would make it easier for people with MS (and neurologists) to navigate and understand treatment options.<br><br>Scoping documents should follow what is generally used in appraisal models as classifications, which is relapsing MS and highly active relapsing MS. This is further broken down by people who are intolerant to, or have relapses on, their first line treatment. | comparators have been updated. In addition, NICE is working with the Association of British Neurologists and NHS England to produce an implementation support tool that aims to clarify the terminology used in the technology appraisal guidance. It will be published on NICE website when complete. |
| | Multiple Sclerosis Trust | While the treatments listed are those that would be offered for relapsing MS, we do not agree with the drugs included in the groupings.<br>**For people with relapsing-remitting MS** | Comments noted. The subgroups and relevant comparators have been updated. |

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| | | We do not believe that cladribine and daclizumab should be included in this group. Both are approved for people whose MS is rapidly evolving severe or highly active despite treatment.<br>**For people with rapidly evolving severe RRMS**<br>We believe this is correct<br>**For people with highly active RRMS despite previous treatment**<br>This group should include cladribine**.**<br>**For people with SPMS with active disease**<br>We believe this is correct<br>The subgroups of comparators listed have become increasingly complex and are not as mutually exclusive as these lists suggest. The use of the drugs within their licensed indications and NICE TAs overlaps to a much greater extent than these subgroups suggest. For example, for people who continue to relapse despite treatment, there may be good reason for a 'lateral' switch to agents of broadly similar efficacy, perhaps due to tolerability or compatibility with personal circumstances. | |
| | Novartis Pharmaceuticals UK Limited | The comparator population "for people with relapsing-remitting multiple sclerosis" is not mutually exclusive from the subgroups "for people with rapidly-evolving severe relapsing-remitting multiple sclerosis" and "for people with highly active relapsing-remitting multiple sclerosis despite previous treatment" as this population can also include people from these subgroups. Teriflunomide and dimethyl fumarate are explicitly not recommended by NICE in those subgroups and the suggested population does therefore not follow current NICE recommendations listed in the Background section of the Draft Scope.<br>The suggested population may lead to inappropriate comparisons and with some populations not being mutually exclusive, there is potential for conflicting recommendations. To avoid a mixed population and maintain | Comments noted. The subgroups and relevant comparators have been updated. |

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| | | consistency with previous NICE recommendations, Novartis suggests replacing “for people with relapsing-remitting multiple sclerosis” with “for people who have active relapsing-remitting multiple sclerosis and do not have highly active or rapidly evolving severe relapsing‑remitting multiple sclerosis”.<br>Regarding the subgroup “secondary progressive multiple sclerosis with active disease, evidenced by relapses”, the ongoing NICE appraisals ID809 and ID937 include interventions (relevant beta-interferons and ocrelizumab) appraised in this subgroup. Therefore, Novartis suggests replacing best supportive care with these relevant comparators as follows:<br><br>For people with secondary progressive multiple sclerosis with active disease, evidenced by relapses<br>• Ocrelizumab (subject to ongoing NICE appraisal)<br>• Relevant beta-interferons (subject to ongoing NICE appraisal) | |
| | Roche Products Ltd | The draft scope includes the following comparators in people with relapsing-remitting multiple sclerosis (RRMS):<br>• alemtuzumab<br>• beta-interferon<br>• cladribine tablets (only if the disease has responded inadequately to treatment with disease-modifying therapy, defined as 1 relapse in the previous year and MRI evidence of disease activity)<br>• daclizumab (only if the disease has been previously treated with at least 2 disease-modifying therapies, and other disease-modifying therapies are contraindicated or otherwise unsuitable)<br>• dimethyl fumarate<br>• glatiramer acetate | Comments noted. The subgroups and relevant comparators have been updated. |

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| | | • teriflunomide<br>• ocrelizumab (subject to ongoing NICE appraisal)<br><br>However, cladribine is only licensed for people with highly active RRMS. As such, the use of cladribine in the RRMS population described in the draft scope would be outside of its marketing authorisation. Cladribine should only be included as comparator for people with rapidly evolving severe RRMS and for people with highly active RRMS despite previous treatment.<br><br>In addition, beta-interferon and glatiramer acetate are subject to ongoing NICE multiple technology appraisal. | |
| | Teva UK Limited | Ocrelizumab and cladribine are not currently standard treatments used in the NHS. Indeed, as noted in the draft scope, ocrelizumab is subject to ongoing NICE appraisal. | Comment noted. These technologies are now recommended by NICE. No action required. |
| Outcomes | ABN | Yes (does freedom from disease activity include MRI measures? | Comment noted. The outcomes in the scope are broad and overarching, more specific outcomes relevant to these broader outcome headings can be considered as part of the appraisal process. |
| | Celgene Ltd | The outcome measure “freedom from disease activity”, which is more recently recognised in the clinical community as NEDA (no evidence of | Comment noted. The outcomes in the scope are broad and |

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| | | disease activity), includes several key components within this one overall composite measure.<br><br>Celgene requests that two components, namely MRI (including T2 lesions, gadolinium-enhancing T1 lesions and brain atrophy) and confirmed disability progression (CDP) should be listed as individual components in the list. | overarching, more specific outcomes relevant to these broader outcome headings can be considered as part of the appraisal process. |
| | Merck | Outcomes are appropriate and consistent with prior appraisals | Comment noted. No action required. |
| | MS Society | To gain a fuller understanding of disease activity a broader range of indicators should be acknowledged, both clinical and subclinical. Understanding of disease activity in MS is evolving, with greater emphasis being placed on symptoms beyond relapse rates and disability progression, such as the number of lesions on MRI scans and brain atrophy. We recommend that these indicators are also included.<br><br>Further indicators should also be included. In 2015, a panel of MS experts proposed the inclusion of measures of cognition, fatigue and depression in the definition of disease activity, patient-reported outcomes that contribute substantially towards quality of life in people with MS. (Brain Health Report) | Comments noted. The outcomes in the scope are broad and overarching, more specific outcomes relevant to these broader outcome headings can be considered as part of the appraisal process. |
| | Multiple Sclerosis Trust | Outcome measures do not include lesion count.<br>Freedom from disease activity is an evolving concept in MS which recognises clinical measures of disease activity, such as relapse rate, but also recognises the critical importance of subclinical disease activity, such as the number of lesions on MRI scans. For every relapse there are approximately 10 MRI lesions that occur asymptomatically. For every visible white matter lesion there are many more microscopic white matter lesions. | Comments noted. The outcomes in the scope are broad and overarching, more specific outcomes relevant to these broader outcome headings can be |

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| | | As there is not yet a fully settled definition of freedom from disease activity, we would recommend that number of lesions on MRI scan is separated out and included as a prime outcome measure of subclinical disease activity.<br>Symptoms - assessment tools for symptoms such as fatigue and cognition in MS is still an evolving area. Multiple instruments are currently in use across clinical trials in MS and it will be important to critically consider the choice of tools as well as the results they demonstrate in the data submitted.<br>There is increasing recognition that in addition to using EDSS as a measure of disability, upper limb function should also be considered, using the nine hole peg test as an outcome measure. | considered as part of the appraisal process. |
| | Teva UK Limited | No comments | Comment noted. No action required. |
| Economic analysis | ABN | Appropriate | Comment noted. No action required. |
| | Celgene Ltd | No comments. | Comment noted. No action required. |
| | Merck | No comments. | Comment noted. No action required. |
| | MS Society | The statement, "costs will be considered from an NHS and Personal Social Services perspective" does not adequately address the personal costs to patients and carers or to society and the economy more broadly.<br><br>MS can have a devastating effect on a person's ability to get into or remain in employment. Research suggests that 80% of people with MS retire within 15 years of diagnosis.[1] Data from the MS Society's My MS My Needs 2 survey (2016) suggests that being on a DMT was a factor in people with MS | Comments noted. In line with NICE reference case, costs are considered from the NHS and Personal Social Services perspective. The committee, at its |

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| | | being in work; people with MS taking a DMT were more likely to be working both full-time and part-time than those who were not.[2]<br><br>MS can also have an impact on unpaid carers' ability to get into or remain in employment. Our research shows that almost 60% of people with MS could need care and support with everyday tasks, 85% of which told us that they receive some level of unpaid care from a friend or family member.[3] Research from the London School of Economics has shown a £5.3bn cost to the economy in lost earnings of carers giving up work to care.[4] The person with MS being on the right treatment that slows disease progression could feasibly limit the extent of the demand for unpaid care and therefore the impact on unpaid carers' employment prospects.<br><br>**Footnotes**<br>1. Zwibel, H. (2009) Health and quality of life in patients with relapsing multiple sclerosis: making the intangible tangible. Journal of the Neurological Science, 287, S11-S16.<br>2. NB All data from My MS My Needs 2 about DMTs refers to people with relapsing forms of MS who could potentially benefit from taking them<br>3. Redfern-Tofts, D., Wallace, L. and McDougal, A. (2016) My MS, My Needs 2: technical report<br>4. Pickard L (2012) Public Expenditure Costs of Carers Leaving Employment. LSE Health and Social Care Blog. London School of Economics & Political Science, 25 April 2012 at: http://blogs.lse.ac.uk/healthandsocialcare/2012/04/25/dr-linda-pickard-public-expenditure-costs-of-carers-leaving-employment/ | discretion, may request non-reference case analyses if appropriate. No action required. |
| | Multiple Sclerosis Trust | The draft scope states that costs will be considered from an NHS and Personal Social Services perspective. With more examples of integrated health and social care budgets, economic cases based on a distinction between the two cost domains are less relevant for commissioners and | Comments noted. In line with NICE reference case, costs are considered from the NHS and Personal |

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| | | payers. There is greater scope for recognising that costs avoided in social care should be included in analysis of a healthcare intervention.<br><br>Economic analysis does not take into account the societal costs of relapses. Relapses have a significant impact on the ability to work or undertake normal daily activities. This is likely to lead to time off work (and potentially loss of employment) both for the person with MS and informal carers, resulting in a loss of productivity. | Social Services perspective. The committee, at its discretion, may request non-reference case analyses if appropriate. No action required. |
| | Teva UK Limited | Within the scope the following is stated: "*For the comparators, the availability and cost of biosimilars should be taken into account*." Teva requests that NICE clarifies this statement regarding the inclusion of follow-on glatiramer acetate in this Appraisal, as glatiramer acetate is a non-biological complex drug and hence the term 'biosimilar' is not applicable for follow-on glatiramer acetate. | Comments noted. The technology appraisal on interferon beta and glatiramer acetate has been updated. No action required. |
| Equality and Diversity | ABN | No | Comment noted. No action required. |
| | Merck | No comments. | Comment noted. No action required. |
| | Multiple Sclerosis Trust | No equality issues to highlight. | Comment noted. No action required. |
| | Teva UK Limited | No comments | Comment noted. No action required. |
| Innovation | ABN | No, similar mechanism of action to fingolimod, which is already available | Comment noted. The appraisal committee will discuss the potentially innovative nature of this |

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| | | | technology. No action required. |
| | Celgene Ltd | Clinical feedback has suggested ozanimod would bring a clinically relevant combination of high efficacy benefit, alongside convenience for the patient due to an oral dosing regimen, respecting MS service pressures and providing the flexibility of rapid reversal in clinical complex situations. Celgene therefore considers ozanimod to be an innovative technology.<br><br>Furthermore, the two Phase 3 ozanimod studies have reported consistent, significant benefits over an active comparator standard of care on the rates of brain volume loss and more specifically deep grey matter regions (cortical and thalamic). The latter regional outcomes have been recognised recently as stronger predictors of longer term disability (Eshaghi et al., Ann Neurol. 2018 Jan 13). The significance of this point has been raised by clinical experts, who have acknowledged the challenges of measuring short term disability progression in more modern MS clinical trial populations, recruiting patients earlier on in the disease course. This benefit is unlikely to be captured by the QALY.<br><br>The majority of high efficacy disease modifying treatments have comparatively long half-lives or are associated with more prolonged periods of immune reconstitution over weeks or months. The rapid recovery of lymphocyte count for ozanimod (2-3 days) is potentially relevant in clinical situations such as infections or in consideration of future treatment sequencing options (Roman et al., J Am Assoc Nurse Pract. 2017 Oct;29(10):629-638). Furthermore, studies have shown that the use of higher efficacy DMTs earlier in therapy results in improved long-term outcomes (Giovannoni G et al., Mult Scler Relat Disord. 2016 Sep;9 Suppl 1:S5-S48), however, many high efficacy DMTs have risk/benefit profiles or tolerability concerns that limit their use to highly active or later line patients | Comments noted. Innovation will be considered by the appraisal committee when formulating its recommendations. The company will have an opportunity to provide evidence on the innovative nature of its product in its submission. No action required. |

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| | | (e.g., fingolimod, natalizumab; Gilenya EPAR summary for the public (EMA Feb 2018); Tysabri EPAR summary for the public (EMA May 2017).<br><br>Furthermore, the recently updated McDonald MS diagnostic guidelines (Thompson AJ et al., Lancet Neurol. 2018 Feb;17(2):162-173) have articulated clear clinical concerns within the MS community in balancing early accurate diagnosis with early treatment intervention, given the recognised challenges of MS and the risk of misdiagnosis. These concerns, further emphasise the importance of additional treatment options, which offer comparatively rapid reversibility in days, alongside therapies with slower reversibility over weeks or months.<br><br>Clinical expert feedback has indicated that there remains a need for additional convenient and well-tolerated once daily oral treatments to ensure long term adherence and sustained disease control. Of note, the ozanimod Phase 3 clinical trial data has supported a favourable tolerability profile, in line with beta interferon. Most recently, data from the real world international MSBase registry has shown that therapies with known tolerability issues, such as dimethyl fumarate, have suboptimal persistence to therapy over 5 years (Spelman T et al., P1193 ECTRIMS 2017).<br><br>These points align with the spirit of the MS trusts' MS forward view consensus statements centred around making the disease modifying treatment services more efficient and convenient (Croft A et al., MS forward view: a consensus for the future of MS services, Nov 2016). | |
| | Merck | No comments. | Comment noted. No action required. |

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| | Multiple Sclerosis Trust | Yes, ozanimod has proven to be effective in clinical trials, and has a convenient, once daily oral dosing schedule. Another drug of the same class, fingolimod, causes temporary changes in heart rate; the first dose of fingolimod is taken under medical supervision to monitor cardiac changes. Ozanimod does not appear to cause these changes and will not require supervision when initiating treatment. | Comments noted. The appraisal committee will discuss the potentially innovative nature of this technology. No action required. |
| | Teva UK Limited | No comments | Comment noted. No action required. |
| Other considerations | Merck | No comments. | Comment noted. No action required. |
| | MS Society | There are also a number of people with primary progressive MS who have disease activity, evidenced by relapses that are not mentioned when further unpacking relapsing MS in the comparator section. | Comment noted. The subgroups included in the scope in the comparator section describe relapsing forms of multiple sclerosis and therefore excludes primary progressive multiple sclerosis which is characterised by gradual worsening of symptoms, rather than relapses. No action required. |

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| | Novartis Pharmaceuticals UK Limited | Regarding the suggested subgroups, Novartis suggests the same changes as listed in the Comparators section. | Comment noted. No action required. |
| | Teva UK Limited | No comments | Comment noted. No action required. |
| Questions for consultation | ABN | Is ozanimod expected to be used to treat secondary progressive MS with active disease evidenced by relapses **yes**<br>Rapidly-evolving severe RRMS **yes**<br>Highly active RRMS despite previous treatment **yes**<br>**And active RRMS**<br><br>Have all relevant comparators been included in the scope **yes**<br><br>Which treatments are considered to be established clinical practice in the NHS for RRMS? **Listed in proposal**<br><br>Secondary progressive MS with active disease evidenced by relapses **Beta interferon**<br><br>How should best supportive care be defined? **Multi-disciplinary care with access to MS consultant, nurse specialist, physio, OT, SALT, dietician, neuropsychology, bladder and bowel management**<br><br>Are the outcomes listed appropriate? **Yes** | Comments noted. The subgroups and relevant comparators have been updated.<br>In line with NICE reference case, costs are considered from the NHS and Personal Social Services perspective. The committee, at its discretion, may request non-reference case analyses if appropriate. |

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| | | Are the subgroups suggested appropriate? **Yes**<br><br>Where do you consider ozanimod for relapsing forms of MS will fit into the existing NICE pathway? **As a first and second line treatment for RRMS and HARRMS (similar MOA drug Fingolimod only approved for use as a second line agent)**<br><br>Equality – no concerns<br><br>Do I consider that the use of ozanimod can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation? **Reduction in working time lost**<br><br>Available data? **Radiance phase 3 study, Sunbeam phase 3 study, not yet published (although preliminary results released) so our opinion is provisional**<br><br>Do I consider there will be any barriers to adoption? **No**<br><br>Would it be appropriate to use the cost comparison methodology for this topic – **Yes**<br><br>Is the new technology likely to be similar in clinical efficiency and resource use to any of the comparators? **Yes – particularly fingolimod**<br><br>Is the primary outcome that was measured in the trial still clinically relevant? **Yes** | |

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| | | Is there any substantial new evidence for the comparator technologies that has not been considered? **No**<br><br>Are there any important ongoing trials reporting in the next year? **Full data from Radiance and Sunbeam trials** | |
| | Celgene Ltd | Is ozanimod expected to be used to treat:<br>• secondary progressive multiple sclerosis with active disease, evidenced by relapses?<br>**The anticipated indication for Ozanimod is for [redacted] Celgene proposes SPMS is removed from the scope as it is not covered within the anticipated licensed indication.**<br>• rapidly-evolving severe relapsing-remitting multiple sclerosis? **Yes.**<br>• highly active relapsing-remitting multiple sclerosis despite previous treatment? **Yes.**<br><br>Have all relevant comparators for ozanimod been included in the scope?<br>**Please see comments within the 'Comparators' section of this response. Celgene would welcome the opportunity to discuss the decision problem, given that the subpopulations currently proposed within the draft scope do not align with those of previous Final Scopes for RRMS and comparators within the proposed subgroups do not align with NICE recommendations, EMA labels or clinical practice.**<br><br>Which treatments are considered to be established clinical practice in the NHS for: | Comments noted. The subgroups and relevant comparators have been updated.<br>Innovation will be considered by the appraisal committee when formulating its recommendations. The company will have an opportunity to provide evidence on the innovative nature of its product in its submission. No action required. |

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| | | • relapsing-remitting multiple sclerosis?<br>**In order for this scope to be aligned with previous RRMS Technology Appraisals, it is recommended that subpopulations are aligned with those as proposed in the 'Comparators' section of this response as are treatments, as follows:**<br>• **For people who have not had previous treatment** (active [non-highly active non-RES] RRMS)<br>o **Beta-interferon [subject to ongoing appraisal]**<br>o **Dimethyl fumarate**<br>o **Teriflunomide**<br>• **For people who have received previous treatment** (active [non-highly active non-RES] RRMS)<br>o **Dimethyl fumarate**<br>o **Teriflunomide**<br>• **For people with rapidly-evolving severe relapsing-remitting multiple sclerosis**<br>o **Alemtuzumab**<br>o **Cladribine**<br>o **Natalizumab**<br>• **For people with highly active relapsing-remitting multiple sclerosis despite previous treatment**<br>o **Alemtuzumab**<br>o **Fingolimod**<br>o **Cladribine** | |

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| | | • secondary progressive multiple sclerosis with active disease, evidenced by relapses? **Subgroup not applicable to proposed Technology Appraisal.**<br><br>How should best supportive care be defined?<br>**Best supportive care will be included within the economic model as in line with previous NICE MS Appraisals.**<br>**Best supportive care is no longer clinically relevant in RRMS, only active comparators. The ozanimod trials were designed vs. active comparator reflecting the ethical principles defined with Good Clinical Practice (GCP).**<br><br>Are the subgroups suggested in 'other considerations appropriate?<br>**Please refer to comments within 'Comparators' section.**<br><br>Are there any other subgroups of people in whom ozanimod is expected to be more clinically effective and cost effective or other groups that should be examined separately?<br>**Until a full clinical and economic assessment of ozanimod has been made based on the final label it is not possible to comment.**<br><br>Where do you consider ozanimod for relapsing forms of multiple sclerosis will fit into the existing NICE pathway, Multiple sclerosis?<br>**Ozanimod's final regulatory label will reflect its appropriate position within clinical practice.**<br>[redacted] | |

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| | | Do you consider ozanimod to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?<br>**Please refer to 'Innovation' section above.**<br>**Clinical feedback has suggested ozanimod would bring a clinically relevant combination of high efficacy benefit, alongside convenience for the patient** due to an oral dosing regimen**, respecting MS service pressures and providing the flexibility of rapid reversal in clinical complex situations**.<br><br>Do you consider that the use of ozanimod can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?<br>Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.<br>**Please refer to 'Innovation' section above.**<br><br>NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on the appropriateness of appraising this topic through this process. (Information on the Institute's Technology Appraisal processes is available at http://www.nice.org.uk/article/pmg19/chapter/1-Introduction).<br>**Appropriate.**<br><br>NICE has published an addendum to its guide to the methods of technology appraisal (available at https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-technology-appraisals/methods-guide- | |

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| | | addendum-cost-comparison.pdf), which states the methods to be used where a cost comparison case is made.<br><br>• Would it be appropriate to use the cost comparison methodology for this topic?<br>**Until a full clinical and economic assessment of ozanimod has been made based on the final label it is not possible to comment.**<br><br>• Is the new technology likely to be similar in its clinical efficacy and resource use to any of the comparators?<br>**Until a full clinical and economic assessment of ozanimod has been made based on the final label it is not possible to comment.**<br><br>• Is the primary outcome that was measured in the trial or used to drive the model for the comparator(s) still clinically relevant?<br>**Both Annualised Relapse Rate and Confirmed Disability Progression were outcome measures captured by the pivotal Phase 3 trials. These are aligned with other clinical trials and key cost-effectiveness model drivers.**<br><br>• Is there any substantial new evidence for the comparator technology/ies that has not been considered?<br>**Not to our knowledge.**<br>Are there any important ongoing trials reporting in the next year?<br>**An open label ozanimod Phase 2 and 3 extension study is ongoing (up to 5 years follow up; NCT02576717).** | |

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| | Merck | No comments. | Comment noted. No action required. |
| | Multiple Sclerosis Trust | **Is ozanimod expected to be used to treat:**<br>• **secondary progressive MS with active disease, evidenced by relapses**<br>It is not clear from the preliminary data published from ozanimod clinical trials whether people with secondary progressive MS (SPMS) were included in trials. Given the difficulty of differentiating between relapsing MS and SPMS with relapses, it is likely that people with SPMS with active disease will be offered ozanimod treatment.<br>We understand that the manufacturer is planning a phase III trial of ozanimod in SPMS, no further details are available.<br>• **rapidly evolving severe RRMS**<br>Yes, subject to marketing authorisation, we might expect this group to be considered for ozanimod treatment.<br>• **highly active RRMS despite previous treatment**<br>Yes, subject to marketing authorisation, we might expect this group to be considered for ozanimod treatment.<br>**Have all relevant comparators been included?**<br>Yes, all the treatments currently approved (or subject to on-going NICE appraisal) for RRMS are included in the scope.<br>**Which treatments are considered to be established clinical practice in the NHS?**<br>All of the treatments would be considered standard clinical practice which recognises that early, proactive treatment is key to preventing disability accumulation.<br>**How should best supportive care be defined?** | Comments noted. The subgroups and relevant comparators have been updated. |

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| | | We do not believe that best supportive care should be included as a comparator; best supportive is the least desirable and least common option for managing relapsing-remitting MS, reserved largely for when all disease modifying therapies are poorly tolerated or the person with MS has expressed a strong and enduring preference for no treatment. There is currently no research or professional consensus on what best supportive care is or how much it costs.<br>Research evidence supports the treatment of people with RRMS early in the disease to prevent axonal damage and irreversible disability.<br>**Where do you consider ozanimod will fit into the existing NICE pathway?**<br>Ozanimod should appear with other disease-modifying therapies under Managing multiple sclerosis. However, we wish to highlight the point made earlier in the section on comparators. Disease modifying treatment of multiple sclerosis is managed in partnership between the prescribing neurologist and the person living with MS. Many of the sub-groups defined in the marketing authorisation and then reflected in previous technology appraisals do not match well with the realities of prescribing in the real world clinical setting. | |
| | Teva UK Limited | None | Comment noted. No action required. |
| | UKMSSNA | Page 1 states that interferons are not recommended, however, we believe that Extavia (an interferon) is?<br><br>Interferons are currently licensed for people with SPMS who also have significant relapses. Therefore should interferons be used as a comparator for ozanimod in SPMS? | Comments noted. The scope has been updated to reflect the appraisals that have now been published. |

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| Additional comments on the draft scope | Merck | No comments. | Comment noted. No action required. |
| | Teva UK Limited | No additional comments | Comment noted. No action required. |

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

Department of Health and Social Care
Sanofi Genzyme