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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Ozanimod for treating relapsing-remitting multiple sclerosis [ID1294]

Appraisal Committee Meeting – 8 April 2021
2nd Committee meeting

The following documents are made available to the Committee:

1. **Appraisal Consultation Document (ACD)** as issued to consultees and commentators

2. **Comments on the Appraisal Consultation Document from Celgene UK Ltd**

3. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   - Multiple Sclerosis Society
   - Multiple Sclerosis Trust
   - Association of British Neurologists
   - Novartis

4. **Comments on the Appraisal Consultation Document from experts:**
   - Lorraine Hazlehurst – Patient Expert, nominated by Multiple Sclerosis Society
   - Dr Eli Silber, Neurologist – Clinical Expert, nominated by Multiple Sclerosis Trust

5. **Comments on the Appraisal Consultation Document received through the NICE website**

6. **Evidence Review Group critique of company comments on the ACD**

7. **Appraisal Committee Meeting presentation slides** – to follow

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Ozanimod for treating relapsing–remitting multiple sclerosis

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using ozanimod in the NHS in England. The appraisal committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, clinical experts and patient experts.

This document has been prepared for consultation with the consultees. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the consultees and commentators for this appraisal and the public. This document should be read along with the evidence (see the committee papers).

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

Issue date: January 2021

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The appraisal committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the committee will also consider comments made by people who are not consultees.
- After considering these comments, the committee will prepare the final appraisal document.
- Subject to any appeal by consultees, the final appraisal document may be used as the basis for NICE's guidance on using ozanimod in the NHS in England.

For further details, see NICE's guide to the processes of technology appraisal.

The key dates for this appraisal are:

Closing date for comments: 10 Feb 2021

Second appraisal committee meeting: TBC

Details of membership of the appraisal committee are given in section 5

1 Recommendations

1.1 Ozanimod is not recommended, within its marketing authorisation, for treating relapsing–remitting multiple sclerosis in adults with clinical or imaging features of active disease.

1.2 This recommendation is not intended to affect treatment with ozanimod that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

Why the committee made these recommendations

Disease-modifying treatments for relapsing–remitting multiple sclerosis include alemtuzumab, beta interferons, cladribine, dimethyl fumarate, fingolimod, glatiramer acetate, natalizumab, ocrelizumab and teriflunomide. Treatments aim to reduce the number of relapses, slow the progression of disability and maintain or improve quality of life.

Clinical trial evidence shows that ozanimod reduces the number of relapses and brain lesions compared with interferon beta-1a. However, ozanimod's effect on the progression of disability is unclear. It is uncertain how effective ozanimod is compared with other treatments because there is no evidence directly comparing them.

The cost-effectiveness estimates are uncertain because of limitations in the clinical effectiveness evidence and are above what NICE normally considers an acceptable use of NHS resources. Therefore, ozanimod is not recommended.

2 Information about ozanimod

Marketing authorisation indication

2.1 Ozanimod (Zeposia, Celgene) is indicated for 'the treatment of adult patients with relapsing remitting multiple sclerosis with active disease as defined by clinical or imaging features'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics.

Price

2.3 The list price for ozanimod is (prices exclude VAT; company submission):

- £343.25 per initiation pack: 4 capsules containing 0.25 mg ozanimod hydrochloride (equivalent to 0.23 mg of ozanimod) and 3 capsules containing 0.5 mg ozanimod hydrochloride (equivalent to 0.46 mg of ozanimod)
- £1,373 per maintenance pack of 28 capsules, each containing 1 mg ozanimod hydrochloride (equivalent to 0.92 mg of ozanimod).

The company has a commercial arrangement, which would have applied if the technology had been recommended.

3 Committee discussion

The appraisal committee considered evidence submitted by Celgene, a review of this submission by the evidence review group (ERG), NICE's technical report, and responses from stakeholders. See the committee papers for full details of the evidence.

Treatment pathway, population and comparators

Ozanimod is likely to be used as a first- or second-line treatment for active relapsing–remitting multiple sclerosis

3.1 Ozanimod's marketing authorisation is for active disease, as defined by clinical or imaging features. The company explained that the ozanimod clinical trials included people who had active disease, defined as:

- at least 1 relapse within the past year or
- at least 1 relapse within the last 2 years and evidence of at least 1 gadolinium-enhancing lesion in the last year.

The company originally positioned ozanimod as a first-line treatment, stating it would not be used for highly active or rapidly evolving severe disease. So it chose the comparators for this appraisal accordingly (see section 3.3). The ERG agreed with the company's positioning of ozanimod. At technical engagement the company updated its positioning of ozanimod to:

- a first-line treatment when infusion or injectable treatments are not suitable because of administration issues or when oral treatments are preferred and
- a second-line treatment when the disease has not responded to 1 or more infusion or injectable treatment.

The clinical experts agreed that ozanimod would be of value as a first-line treatment, because there are no oral drugs available as first-line treatment for people who have only had 1 relapse in the last 2 years. They also recognised that ozanimod would be useful as a second-line treatment as another option to fingolimod, the only sphingosine-1-phosphate receptor (S1PR) modulator currently available for relapsing–remitting multiple sclerosis. Ozanimod is also an S1PR modulator and does not have the same cardiac side effects as fingolimod. Having another first- and second-line treatment option would offer people more choice. The company's

submission states that ozanimod is not likely to be used in highly active disease. However, this subtype of multiple sclerosis is often defined as disease that has inadequately responded to disease-modifying therapy. So, the company's positioning of ozanimod as a second-line treatment implies it would be used for highly active disease. The clinical experts explained that multiple sclerosis categorisations are not always clearly defined and can be complex in clinical practice. The committee concluded that ozanimod was likely to be used as a first- or second-line treatment in people who have active relapsing–remitting multiple sclerosis.

It is not appropriate to limit the population to people for whom an oral treatment is suitable or who request an oral treatment

3.2 The population in the company's submission was originally people with relapsing–remitting multiple sclerosis. Later the company restricted this population to include only people with active relapsing–remitting multiple sclerosis for whom an oral treatment is suitable or who request one. The committee accepted that 'active' was added to update the population in line with ozanimod's marketing authorisation, which was granted after the company's submission was received. The company explained that it restricted the population to people for whom an oral treatment is suitable or who request one because it considered this is how it would be used in practice. It estimated that the oral drugs teriflunomide and dimethyl fumarate account for around 50% of the market share in relapsing–remitting multiple sclerosis treatments, and ozanimod would most likely be used in their place. However, the NHS commissioning expert said that based on the data available, 50% market share was likely to be a significant overestimate. The clinical experts explained that it would be very difficult to identify a group of people for whom only oral treatments are suitable. They agreed that many people would choose an oral drug over an injection or infusion, but highlighted that people often switch between treatments with different routes of administration. The patient experts stated that there are many reasons why someone would change their mind about their treatment. Also, they would not want to be excluded

from having a treatment because of its route of administration. The ERG also had concerns about restricting the population, explaining that it was unclear what is meant by people for whom an oral treatment is suitable or who request one. The committee was concerned that restricting the population would exclude potential comparators that are routinely used in the NHS. It concluded that it was not appropriate to limit the population to people for whom an oral treatment is suitable or who request an oral treatment.

All first-and second-line treatments used for active relapsing–remitting multiple sclerosis, including ocrelizumab, are comparators

3.3 In its submission, the company included beta interferons (1a and 1b), dimethyl fumarate, glatiramer acetate, teriflunomide and peginterferon beta-1a as comparators. Alemtuzumab and ocrelizumab were included in the scope, but the company excluded them as comparators in its base-case analysis (although it provided analyses with them as comparators in an appendix). Alemtuzumab was excluded because a safety review restricted its use to highly active disease, and ozanimod was not expected to be used in highly active disease. Ocrelizumab was excluded because NICE only recommends it when alemtuzumab is contraindicated or otherwise unsuitable. However, clinical experts advising the ERG and the clinical experts at the meeting confirmed that ocrelizumab is being used as a first-line treatment for relapsing–remitting multiple sclerosis in the NHS. For the restricted population (see section 3.2), the company's only comparators were dimethyl fumarate and teriflunomide. This was because these are the only oral drugs used as first-line treatment for active relapsing–remitting multiple sclerosis. The ERG did not agree with the company restricting the population and having only dimethyl fumarate and teriflunomide as comparators. The committee agreed with the ERG that all the company's original comparators, plus ocrelizumab, are relevant comparators for first-line treatment. Also, the company and experts had explained that ozanimod could also be used as a second-line treatment when relapsing–remitting multiple sclerosis has not responded to 1 or

more of the infusion or injectable treatments (see section 3.1). So, the committee considered second-line treatments to also be comparators, several of which had not been included by the company. The committee concluded that all first- and second-line treatments used for active relapsing–remitting multiple sclerosis, including ocrelizumab, were comparators.

Ozanimod clinical trials

Baseline characteristics in the trials are generalisable to people in the NHS with active relapsing–remitting multiple sclerosis

3.4 The phase 3 trials RADIANCE part B and SUNBEAM compared ozanimod with interferon beta-1a. The trials had very similar designs, inclusion and exclusion criteria and outcomes, but differed in duration (RADIANCE part B had a 24-month follow-up period, whereas SUNBEAM had a 12-month follow-up period). The ERG considered that although the baseline characteristics of people in the trials were broadly generalisable to people having treatment in the NHS, there were some characteristics that may limit generalisability. For example, around 23% of people in the trials had highly active or rapidly evolving severe relapsing–remitting multiple sclerosis and about 30% had already had a prior disease-modifying therapy. The ERG explained that this was not in line with the company submission but may have become less of an issue since the company updated ozanimod's positioning to a second-line treatment. The ERG also highlighted that there was a higher proportion of people of white family origin and from Eastern Europe than in the NHS population. The clinical experts advised that the trial population and the more diverse population in NHS practice were likely to have a similar natural history of relapsing–remitting multiple sclerosis. They therefore considered the baseline characteristics in RADIANCE part B and SUNBEAM to be generalisable to NHS practice. The committee concluded that the baseline characteristics in RADIANCE part B and SUNBEAM were generalisable to people in the NHS with active relapsing–remitting multiple sclerosis.

Ozanimod reduces relapses and brain lesions compared with interferon beta-1a, but its effects on disability progression are uncertain

3.5 In RADIANCE part B and SUNBEAM, the primary outcome was annualised relapse rate. Key secondary outcomes included:

- number of new or enlarging hyperintense T2-weighted brain MRI lesions
- number of gadolinium-enhanced T1 brain MRI lesions and
- time to onset of confirmed disability progression (CDP) after 3 months (CDP-3M) and after 6 months (CDP-6M).

The committee confirmed that in previous appraisals it had preferred to use CDP-6M instead of CDP-3M because CDP-6M is a more robust measure of disability progression and is less likely to be influenced by relapses. Ozanimod was effective at reducing relapses compared with interferon beta-1a in RADIANCE part B, SUNBEAM and a pooled analysis using 12-month data from each trial. It was also better than interferon beta-1a for both MRI outcomes. However, there was no statistically significant difference between ozanimod and interferon beta-1a for either CDP outcome. The company explained that ozanimod's benefits may have been underestimated because there were low rates of CDP in both treatment arms in the trials. This meant there was high variability and a wide statistical range in the results, and a reduced ability to detect a meaningful difference in CDP between treatments. The company also requested that the CDP results be considered alongside other outcomes for which ozanimod had been shown to be more effective than interferon beta-1a, that is, annualised relapse rate and brain MRI lesions. This was because it considered it implausible that ozanimod could be worse than interferon beta-1a for CDP outcomes but better for relapse and MRI outcomes. It also suggested that CDP was a less important outcome in clinical practice than in clinical trials and cost-effectiveness models. The ERG highlighted the relative difference in CDP between ozanimod and interferon beta-1a. It also noted that the rates of CDP-6M were lower with

interferon beta-1a than ozanimod in both trials (as shown by a hazard ratio greater than 1 for ozanimod compared with interferon beta-1a) but the difference was not statistically significant. The clinical experts explained that a treatment that reduced MRI activity and relapses would also be expected to reduce CDP. They considered that the people enrolled in RADIANCE part B and SUNBEAM may have milder relapsing–remitting multiple sclerosis than average. So, they would be less likely to progress in terms of disability over the short duration of the trials. The clinical experts thought it unlikely that ozanimod would be worse than interferon beta-1a for CDP outcomes. They noted that interferon beta-1a is usually considered as having lower efficacy than some of the other available treatments. The NHS commissioning expert confirmed this view. Considering the expert statements and trial evidence, the committee concluded that ozanimod was effective at reducing relapses and brain lesions compared with interferon beta-1a, but its effects on disability progression were uncertain.

Indirect treatment comparison

The company's network meta-analysis is generally well conducted, but should account for variability

3.6 The company did a Bayesian network meta-analysis (NMA) to estimate ozanimod's relative effectiveness compared with all comparators in the scope. It modelled annualised relapse rate, CDP-3M, CDP-6M, treatment discontinuation, adverse events and serious adverse events. Some older studies did not report CDP-6M so the company also analysed CDP-3M and -6M combined in a single model so that CDP-6M could be predicted for all comparators. In this analysis it assumed that the hazard ratios for CDP-6M between treatments were proportional to the hazard ratios for CDP-3M between treatments. The ERG considered the company's approach to the NMA to be generally appropriate. It was satisfied that any heterogeneity or inconsistency did not have an important effect on results. It did, however, highlight that the assumption of a linear relationship

between the CDP-3M and CDP-6M hazard ratios for ozanimod appeared to have been violated and advised caution when drawing conclusions from the company's CDP-6M combined analysis. The committee noted the ERG's concerns and preferred the CDP-6M NMA estimated from the trial data directly, rather than the combined CDP-6M NMA that was estimated from the CDP-3M data. The company explained that the proportional relationship between CDP-3M and CDP-6M in its combined analysis was assumed to be fixed and to be the same for all studies and treatments. The committee considered it would have preferred for between-study or between-treatment variability, or both, to have been accounted for in the company's combined CDP-6M NMA. The ERG identified a potential issue with the glatiramer acetate 40 mg CDP data used in the company's NMA. It explained that the company may have made an error in data extraction, in which CDP at 12 months may have been extracted as CDP at 12 weeks by mistake. The ERG suspected this data had then been used in the CDP-6M combined analysis in the company's NMA. The company could not confirm whether there had been an error in data extraction for glatiramer acetate 40 mg. Therefore the committee interpreted the results for this comparator with caution. It concluded that the company's NMA was generally well conducted but should have accounted for between-study or between-treatment variability, or both.

The company's cost–utility model

The company's model is generally appropriate and aligns with previous models in the disease area

3.7 The company's model structure was similar to that of models used in previous multiple sclerosis technology appraisals. The model was a Markov transition model consisting of 21 health states (10 Expanded Disability Status Scale [EDSS] states for relapsing–remitting multiple sclerosis, 10 for secondary progressive multiple sclerosis, and death). The model used the British Columbia Multiple Sclerosis registry as a source of

natural history data. Treatment effects for ozanimod and all comparators were obtained from the company's NMA and applied as:

- annualised relapse rates
- CDP-6M (using the combined outcome, see section 3.8)
- adverse events and
- treatment discontinuation (see section 3.9).

The company incorporated a treatment waning effect for all treatments and explained that no treatment switching was allowed in its model. The ERG highlighted that the lack of treatment switching or sequencing in the model may over-simplify what happens in NHS practice. However, it acknowledged that a model that can simulate treatment switching or treatment sequencing would be complex to construct, and difficult to populate because of limited data. The committee acknowledged the lack of treatment switching as a limitation of the model. It concluded that the company's model was generally appropriate and in line with previous models in the disease area.

Ozanimod's disability progression hazard ratio from the NMA should be used, rather than the interferon beta-1a hazard ratio

3.8 The company explained that it had used the combined CDP-6M outcome from its NMA to model the effects of treatments on disability progression. It had advised about the issues with the CDP data in the ozanimod clinical trials (see section 3.5) and noted that these trial results underpinned the NMA results for ozanimod. The company also explained that it set ozanimod's CDP-6M hazard ratio as equal to the CDP-6M hazard ratio for interferon beta-1a in its model, which it considered to be a conservative assumption. This was because it considered it would be implausible that using interferon beta-1a could lead to a lower rate of disability progression than ozanimod (see section 3.5). The ERG highlighted that the company had only set ozanimod as equivalent to interferon beta-1a for CDP-6M and not for relapses, and this was inconsistent. It further highlighted that

the point estimate in the NMA suggested that ozanimod was not as beneficial as interferon beta-1a for CDP-6M. Also, there are other drugs available that have been shown in clinical trials to work better than interferon beta-1a for this outcome. The committee recognised that the clinical experts suspected the non-statistically significant CDP-6M results in the ozanimod trials could be because of milder disease and short trial duration. That is, not because ozanimod does not work as well as interferon beta-1a for this outcome (see section 3.5). However, the committee also understood that the ozanimod trials were of high quality. So, given the uncertainty and for consistency with other outcomes, the committee considered that ozanimod's CDP-6M hazard ratio from the NMA should be used. The committee also considered that the NMA results estimated directly from the CDP-6M trial data, rather than the CDP-6M results from the combined outcome estimated from the CDP-3M data, should be used in the model when possible (see section 3.6). The committee concluded that ozanimod's disability progression hazard ratio from the NMA should be used, rather than the interferon beta-1a hazard ratio.

Both the company's and ERG's approaches to modelling treatment discontinuation have limitations

3.9 The company's cost–utility model did not allow people to switch between treatments, so people were assumed to only have 1 disease-modifying treatment. The company took rates of discontinuation for each treatment from its NMA. It assumed that the rate of discontinuation was the same over the entire model time horizon. People stopped treatment if they reached EDSS state 7 or above, developed secondary progressive multiple sclerosis or died. The ERG preferred a different approach. Its clinical advisers suggested that if no switching of treatments were allowed (as was the case in the model), people would only stop treatment if they were no longer benefitting, even if they still had relapses. Based on this, the ERG used trial treatment discontinuation rates when possible, then assumed everyone stayed on treatment until they reached EDSS state 7

or above, developed secondary progressive multiple sclerosis or died. The clinical experts explained that it was difficult to determine whether the company or ERG's approach better represented NHS practice because people usually switch between several disease-modifying treatments over their lifetime. So, neither approach wholly reflected what would happen in practice. The committee considered the lack of treatment switching to be a limitation of the company's model (see section 3.7). It concluded that both the company and ERG's approaches to modelling treatment discontinuation had limitations.

Cost-effectiveness estimate

The most likely cost-effectiveness estimates are outside what NICE normally considers an acceptable use of NHS resources

3.10 Because of confidential commercial arrangements for ozanimod and comparator treatments, the cost-effectiveness results cannot be reported here. However, the cost-effectiveness estimates for ozanimod compared with other first-line treatments for relapsing–remitting multiple sclerosis were outside what NICE normally considers an acceptable use of NHS resources. Also, neither the company nor the ERG's analyses reflected the committee's preferred assumptions, which were likely to increase the incremental cost-effectiveness ratios. The committee noted that although the company had mentioned at technical engagement that ozanimod may be used as a second-line treatment, it had not explained why it had changed its opinion or provided any updated analyses to reflect this. For example, the company's base case only included comparators used as first-line treatment (see section 3.3).

The committee would have preferred to see a cost–utility analysis that:

- uses ozanimod's CDP-6M hazard ratio from the NMA, rather than setting ozanimod as equivalent to interferon beta-1a
- uses the trials' CDP-6M hazard ratios when possible, and only used the combined CDP-6M hazard ratios for treatments that do not have

CDP-6M data available (glatiramer acetate 40 mg [if available; see section 3.6], interferon beta-1a 22 micrograms and peginterferon beta-1a)

- uses combined CDP-6M hazard ratios, when these are used, from an NMA that accounts for between-study or between-treatment variability, or both
- includes comparisons with second-line treatments (alemtuzumab, cladribine, fingolimod and ocrelizumab) if ozanimod is positioned for second-line treatment.

Other factors

3.11 The committee concluded that ozanimod's benefits were adequately captured in the economic analysis so did not consider it innovative.

4 Proposed date for review of guidance

4.1 NICE proposes that the guidance on this technology is considered for review by the guidance executive 3 years after publication of the guidance. NICE welcomes comment on this proposed date. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Sanjeev Patel
Chair, appraisal committee
January 2021

5 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee B.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Hannah Nicholas
Technical lead

Carl Prescott
Technical adviser

Jeremy Powell
Project manager

Joanne Ekeledo
Project manager

ISBN: [to be added at publication]

NICE National Institute for Health and Care Excellence

Ozanimod for treating relapsing-remitting multiple sclerosis [ID1294]

Consultation on the appraisal consultation document – deadline for comments 5pm on 12th February 2021 **email:** 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):	**Celgene**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A

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NICE National Institute for Health and Care Excellence

Ozanimod for treating relapsing-remitting multiple sclerosis [ID1294]

Consultation on the appraisal consultation document – deadline for comments 5pm on 12th February 2021 **email:** NICE DOCS

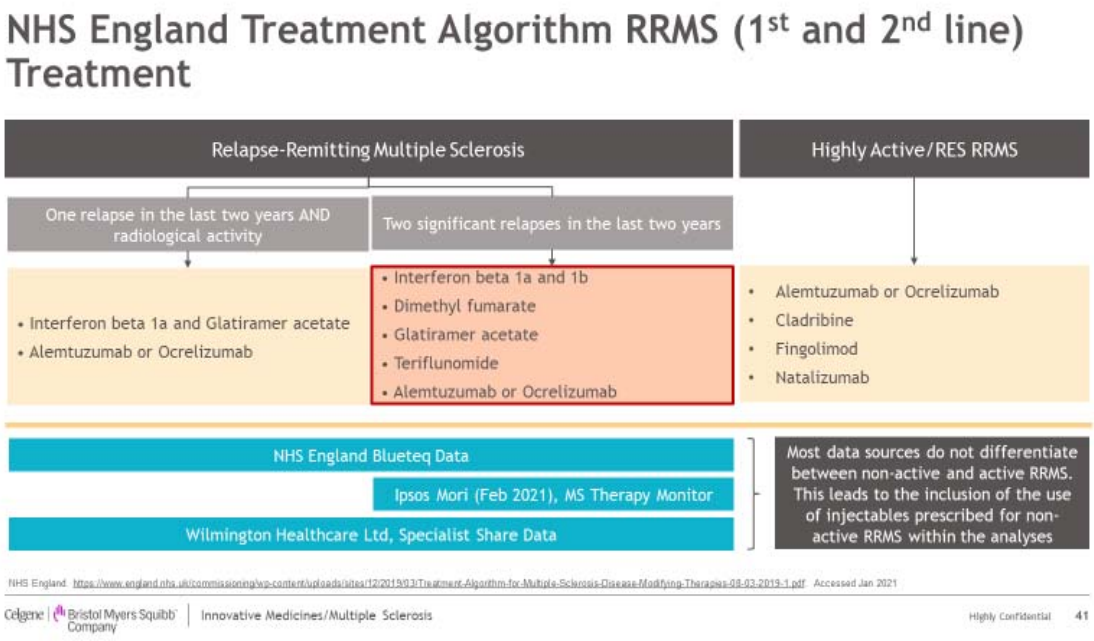
Name of commentator person completing form:	Gabriel Okorogheye
Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that …….. • 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?
1	Celgene welcomes the opportunity to provide comments on the NICE Appraisal Consultation Document (ACD) for ozanimod for treating relapsing-remitting multiple sclerosis (RRMS). We are disappointed that the Committee was unable to recommend ozanimod, particularly since this appears to be based solely on uncertainty around its effectiveness in reducing Confirmed Disability Progression (CDP) without taking into account strong evidence that showed a reduction in the number of relapses and brain lesions. Further to this, the decision appeared to overlook the views of the clinical experts and recommendations from the ERG report. This response will cover these key areas: • Positioning and comparators • Current treatment patterns • Measures of treatment effect • CDP in the economic model
2	**Positioning and comparators** Section 3.1 of the ACD states "*the committee concluded that ozanimod was likely to be used as a first- or second-line treatment in people who have active relapsing–remitting multiple sclerosis."* And that *"The company's submission states that ozanimod is not likely to be used in highly active disease. However, this subtype of multiple sclerosis is often defined as disease that has inadequately responded to disease-modifying therapy. So, the*

	company's positioning of ozanimod as a second-line treatment implies it would be used for highly active disease. Celgene would like to clarify the positioning, since we accept that this might not have been clear in our submissions and, therefore, to the Committee. The population is those patients with **active** RRMS, not those with **highly active** RRMS. We also suggest that ozanimod is most likely to be used in those whose disease is defined in the NHS England MS Treatment Algorithm for RRMS as "2 significant relapses in last 2 years". Accordingly, we propose that any guidance should restrict ozanimod to this population. It encompasses both the *first-line* and *first-switch* settings within this cohort. This position would be comparable to the NICE recommendations for the two other oral medicines (dimethyl fumarate and teriflunomide) prescribed for active RRMS. Every patient in the ozanimod trials was required to have at least 1 relapse within the 12 months prior to screening. In fact, Celgene can confirm that 53% of patients in the pooled analysis had at least 2 relapses in the 2 years preceding the baseline visit, with similar results to the overall trial population. This suggests that the trial population is generalisable to the target population in the NHS England MS Treatment Algorithm of 2 significant relapses in the last 2 years.
3	**Current treatment patterns** As reported in Section 3.1 of the ACD, we "*estimated that the oral drugs teriflunomide and dimethyl fumarate account for around 50% of the market share in relapsing–remitting multiple sclerosis treatments".* Conversely, the NHS commissioning expert thought that 50% market share was likely to be a significant overestimate, based on available data. Although it may be the case that fewer than 50% of ***all*** MS patients are treated with oral drugs, in the population of interest, the proportion is likely to be considerably higher than 50%. The NHS England algorithm defines first-line **active** RRMS therapy as patients that have had 2 significant relapses in the last 2 years. These patients may be prescribed oral DMTs (dimethyl fumarate or teriflunomide), injectable DMTs (Interferon beta 1a and 1b, and glatiramer acetate) or, in exceptional circumstances, ocrelizumab. Celgene believes that within this set of comparators it is appropriate for ozanimod to be compared to other oral DMTs. Injectable DMTs are not routinely prescribed for this patient group due to perceived lower efficacy by clinical teams and are primarily reserved for **non-active** RRMS. Injectable treatments are still used as some patients commenced therapy with them (when oral treatments were not available) or to cover treatment in the case of pregnancy with glatiramer acetate (Dobson R, et al. Pract Neurol 2019;19:106–114).

Ozanimod for treating relapsing-remitting multiple sclerosis [ID1294]

Consultation on the appraisal consultation document – deadline for comments 5pm on 12th February 2021 **email:** NICE DOCS

Below we demonstrate that, in clinical practice, it is oral treatments that are favoured for patients with **active** RRMS (2 significant relapses in last 2 years).



[commercial in confidence information removed]

This would indicate a conservative estimate of around 52% of registrations for oral medicines, as the other medicines can be prescribed in patients with a **non-active** RRMS and **active** RRMS diagnoses[1].

[1] NHS England (Feb 2021), Blueteq data for Multiple Sclerosis, 2019 Registrations data

[academic in confidence information removed]

[commercial in confidence information removed with figure below]

[commercial in confidence information removed with figure below]

	[commercial in confidence information removed with 2 figures below] The above evidence from various sources, demonstrates that oral therapies are the most prescribed class of treatments for **active** RRMS. This result is consistent when all injectable treatments are included, despite the treatments being recommended in both **active** and **non-active** RRMS. The numbers of patients prescribed injectable therapies have declined significantly since the introduction of oral treatments. Those remaining upon injectable treatments are likely to be as a result of legacy prescribing. The estimate of 50% of **active** RRMS patients being treated with oral medicines is accurate when validated with various data sources. In addition, it is expected that this percentage will increase over time based on new incident patients and treatment switches. Based on these findings, the most appropriate comparators for ozanimod would be other oral treatments recommended for use in **active** RRMS patients.
4	**Measures of treatment effect** Section 3.5 of the ACD states "*Ozanimod reduces relapses and brain lesions compared with interferon beta-1a, but its effects on disability progression are uncertain".* To address this uncertainty a discussion is provided with evidence from various MS trials that are relevant to ozanimod. **ARR and MRI Endpoints** In both the SUNBEAM and RADIANCE Phase III clinical trials ozanimod demonstrated superiority to IFN β-1a on ARR (primary endpoint) and MRI endpoints including new/enlarged T2 lesions (measure of cumulative disease) and GdE lesions (active disease/acute inflammation), both key secondary endpoints. SUNBEAM and RADIANCE were powered for the primary endpoint of annualized relapse rate (ARR), not for CDP.[1, 2] Volumetric MRI measures are a well-established surrogate of disability, correlating well with MS-related disease progression, [3] particularly compared with clinical activity in populations with mild MS early in the disease course, such as those in the SUNBEAM and RADIANCE trials. **CDP** There was no statistically significant difference between ozanimod and interferon beta-1a for CDP outcomes from the pooled analysis. This result was a secondary endpoint in the trials. However, not only did both trials not power to detect a difference in this endpoint, they also observed a very low rate of CDP events in both arms, which further hampered the analysis from reaching any statistical significance.

	This low rate of events may be explained by low mean baseline EDSS scores in the ozanimod trials (2.5 and 2.6 respectively in *RADIANCE* and *SUNBEAM*). The clinical expert in the ACM stated that they "[...] *considered that the people enrolled in RADIANCE part B and SUNBEAM may have milder relapsing–remitting multiple sclerosis than average. So, they would be less likely to progress in terms of disability over the short duration of the trials"*. Rates of CDP-6M were especially low in SUNBEAM, likely reflecting the shorter trial duration, which meant tentative disability progression (ie, the initial increase in EDSS score) would have had to develop within ≤6 months of baseline to allow confirmation by 12 months. The ACD acknowledges that *"The clinical experts thought it unlikely that ozanimod would be worse than interferon beta-1a for CDP outcomes*." Of note, approximately 70% of patients in the ozanimod clinical trials were treatment naive. These characteristics are consistent with a population with low likelihood of disability progression. This phenomenon was previously shown in the CARE-MS trials of alemtuzumab, wherein rates of CDP-6M were lower in the treatment-naive patients in CARE-MS I[4] (alemtuzumab, 8.0%; IFN β-1a, 10.7%) compared with previously treated patients in CARE-MS II (alemtuzumab, 12.7%; IFN β-1a, 19.8%).[5] This was also shown in a real-world study of fingolimod wherein CDP-3M occurred in none of the treatment-naive patients versus 8.9% of patients who switched to fingolimod because of drug failure.[6] When looking at treatments reimbursed by NICE for use in **active** RRMS patients who were compared to an active comparator, dimethyl fumarate did not show statistical significance against glatiramer acetate in CDP outcomes. Other treatments in this space such as glatiramer acetate and teriflunomide showed significance in CDP outcomes, but only were the treatments were compared against placebo.[7] **Composite measure** NEDA-3 is a proposed surrogate measure for disease activity–free status[8]. NEDA (no evidence for disease activity) is a combined measure of disease activity based on relapses, disability progression and MRI results. Where patients meet NEDA criteria, they are free from measurable disease activity over a defined period of time. In RADIANCE, a significantly higher proportion of patients treated with ozanimod versus IFN β-1a showed no evidence for disease activity (NEDA-3) after 2 years[9] This would indicate an overall improvement in outcomes when compared to IFN β-1a. Even though modelling used by NICE is driven by CDP, in clinical practice, the reproducibility or reliability of CDP for clinical decision making is considered to be far less meaningful. The Committee should consider other endpoints such as reductions in statistically significant differences in no evidence for disease activity (NEDA), and statistically significant reductions in ARR and brain lesion against an active comparator.

	These endpoints are of importance to determine the clinical effectiveness of ozanimod for patients with **active** RRMS. **References** 1. Comi G, Kappos L, Selmaj KW, et al. Safety and efficacy of ozanimod versus interferon beta-1a in relapsing multiple sclerosis (SUNBEAM): a multicentre, randomised, minimum 12-month, phase 3 trial. Lancet Neurol. 2019;18(11):1009-1020. 2. Cohen JA, Comi G, Selmaj KW, et al. Safety and efficacy of ozanimod versus interferon beta-1a in relapsing multiple sclerosis (RADIANCE): a multicentre, randomised, 24-month, phase 3 trial. Lancet Neurol. 2019;18(11):1021-1033. 3. Jeffery DR, Di Cantogno EV, Ritter S, et al. The relationship between the rate of brain volume loss during first 24 months and disability progression over 24 and 48 months in relapsing MS. J Neurol. 2016;263(2):299-305. 4. Cohen JA, Coles AJ, Arnold DL, et al. Alemtuzumab versus interferon beta 1a as first-line treatment for patients with relapsing-remitting multiple sclerosis: a randomised controlled phase 3 trial. Lancet. 2012;380(9856):1819-1828. 5. Coles AJ, Twyman CL, Arnold DL, et al. Alemtuzumab for patients with relapsing multiple sclerosis after disease-modifying therapy: a randomised controlled phase 3 trial. Lancet. 2012;380(9856):1829-1839. 6. Correia I, Batista S, Marques IB, et al. The effectiveness of fingolimod in a Portuguese real-world population. Mult Scler Relat Disord. 2016;6:41-48. 7. Wiendl et Meuth 2015, Drugs 75:947–977 8. Parks N. NEDA treatment target? No evident disease activity as an actionable outcome in practice. J Neurol Sci. 2017:31-34. 9. Steinman L, Comi G, Cree BA, et al. Higher rates of no evidence of disease activity (NEDA) in relapsing multiple sclerosis patients treated with ozanimod vs interferon beta-1a in the phase 3 RADIANCE trial. Presented at: Consortium of Multiple Sclerosis Centers 2019 Annual Meeting, May 28–June 1, 2019; Seattle, Washington.
5	**CDP in the economic model** As described above, CDP is not only a poor measure in the patient population of interest, it was a secondary endpoint not powered to detect differences between treatment arms. As a result, the ozanimod pooled analysis had approximately 41% power to detect a significant difference in CDP-3M and was underpowered to show a benefit versus IFN β-1a on this endpoint. As such, it provides an inadequate basis for assessing the full benefit of ozanimod. Furthermore, when this endpoint is used within our Network Meta-Analysis (NMA) in order to compare with other treatments the results are, themselves, not statistically significantly different.

	Nevertheless, the model used in this appraisal is the recognised model, accepted by NICE across several appraisals for the other MS treatments, and it is based on CDP. We accept that, perhaps, we could have departed from this model structure but contend that this would have raised other concerns in being able to compare with previous decisions. In such a situation, it is even more vital to take into account the views of experienced clinicians. In fact, although Section 3.5 of the ACD notes that "*the clinical experts thought it unlikely that ozanimod would be worse than interferon beta-1a for CDP outcomes"* this expert opinion been reflected in the ACD and, instead, the Committee selected the worst possible assumptions on CDP for ozanimod. Further, we would like to remind the Committee that the ERG's preferred analysis from the STA report (dated 21 January 2020, updated September 2020, page 75) states "*the ERG considers that the company has potentially produced overly pessimistic relative cost effectiveness results for treatment with ozanimod by modelling differences in effectiveness (namely, CDP-6M combined, ARR, treatment discontinuation rates and SAE rates) between treatments which were shown by results from the company's NMAs not to be statistically significant.* *The ERG considers that when generating base case cost effectiveness results, if clinical effectiveness results are not statistically significantly different, then a difference in effect should not be modelled."* It is disappointing that the ERG report was not mentioned in the public section of the ACM, although it does appear in the ACD. Given that the ERG considered our base case to *underestimate* the treatment effect, it is surprising that the Committee have chosen a set of assumptions that are even more pessimistic. Conversely, if one uses the ERG's amendments to the model so that only statistically significant differences in treatment effect are included, [commercial in confidence information removed] For the comparison of treatment with ozanimod versus DMF [commercial in confidence information removed] [commercial in confidence information included in a table removed] We also note that several appraisals for the same population (TA303, TA320, TA527 and TA624) have been able to conclude that the treatments evaluated in the NMAs were "similar", "similarly effective", "as effective" and/or "there were no differences" in the absence of non-inferiority evidence. It is unclear why, in the case of ozanimod, a different conclusion has been drawn. Further, other treatments that have been recommended for active RRMS have also failed to show statistically significant differences in CDP outcomes when compared with active treatments. (TA303 – teriflunomide, TA320 – dimethyl fumarate, and TA533 –

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	beta interferons/glatiramer acetate). Ozanimod is in a similar situation to those other treatments with regards to CDP, but it *has* shown statistically significant benefits from the reduction of annual relapse rates (primary endpoint) and brain lesions. Again, it is unclear why the decision on ozanimod has departed from those made in previous, similar situations. Taken together, there is a case for a pragmatic decision to be taken which, in the absence of evidence to the contrary, assumes that ozanimod is sufficiently similar to the oral comparators. This approach has been taken in previous MS appraisals and, indeed, for ozanimod in other jurisdictions. In which case, the remaining question is one of cost which, due to the many Patient Access Schemes in place in this setting, is something only Committee and the ERG can assess.

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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
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
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	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	**Relapse rate and disability progression** Ozanimod has been shown in clinical trial to be effective at reducing the number of relapses and the number of brain lesions in relapsing remitting MS, as compared to interferon beta-1a. Rates of confirmed disability progression between the two drug treatments were not significantly different. When choosing to take a disease modifying treatment (DMT), outcomes important to people with MS include a reduction in relapse rate, in disability progression, and a reduction in evidence of active disease. Research has shown the scale of the detrimental impact of relapses on the daily life of people with relapsing remitting MS, and emphasises the importance of relapse reduction as a worthwhile treatment aim. One study reported that the majority of patients required additional support with routine daily tasks during their most recent relapse, with relapse also affecting people's finances and ability to work. Clearly, a new treatment that has been shown to reduce annual relapse rate and other markers of disease would be of value to people with relapsing MS [(1)] The MS Society funded a two-year project entitled "*Considering the Risks and Benefits in Multiple Sclerosis Treatment Decisions*" (CRIMSON) [(2),] which aimed to improve understanding of how people with relapsing MS weigh up the pros and cons of different DMTs. This qualitative research demonstrated the various and interrelated factors informing a person's choice of treatment. Effects on long term disability progression may be seen by some people with MS as relating to future long term health outcomes, whilst relapse reduction can represent a more immediate or shorter-term impact on MS symptoms. A patient expert to the ozanimod NICE Committee with MS, said of her experience of relapse, "*They can be mild to significant in impact, with varying ability to fully recover from them. Sometimes they can be short, mild and you return to your previous health, other times they can be long in length, creates significant impact on you and you do not recover fully".* In terms of disability progression, we note the NICE's clinical experts' statement that the people enrolled in the ozanimod Phase III clinical trials may have had milder relapsing–remitting multiple sclerosis than average, and they would be less likely to progress in terms of disability over the short duration of the trials. The experts' comment that they considered it unlikely that ozanimod would be worse than interferon beta-1a in terms of disability progression outcomes, and that a treatment that reduced relapses and MRI activity of disease would also be expected to reduce confirmed disability progression, is a reasonable one, although we accept the uncertainty around this point. Clearly, longer term outcome data is required, but we would also ask the committee to consider the impact and fairness on people with MS of data assessments that may require people to wait many years for new treatment options. We note that fingolimod for relapsing remitting MS has been approved by NICE for use on

	the NHS. A 2010 study of this drug demonstrated improved annual relapse rates as compared to interferon beta-1a, yet differences in disability progression between the two drugs were not statistically significant. References: 1. The UK patient experience of relapse in Multiple Sclerosis treated with first disease modifying therapies (msard-journal.com) 2. Understanding treatment decisions from the perspective of people with relapsing remitting multiple Sclerosis: A critical interpretive synthesis - White Rose Research Online
2	**The importance of a new oral option** Everyone with MS is different. People with MS require a range of safe and effective treatments which they can take in a way that suits their clinical needs and lifestyle. Whilst oral options may not be suitable for every patient, many people with MS tell us about the convenience of DMTs that can be taken at home. For many people with MS of working age and for those with limited mobility, taking time out of work or having to travel to attend hospital appointments can be challenging. The CRIMSON study of the experience of people with relapsing MS in choosing treatments reported that, "..*treatment compliance is key and PwRRMS need to be able to manage treatment mode and frequency within their own daily regimen and determine what suits them best - daily tablets, or more infrequent induction therapies, or consider the complexities of PwRRMS who need to travel for work and the complexities of managing injections in those circumstances"* Treatment options which do not require clinic or hospital appointments have an obvious advantage during the current coronavirus pandemic, potentially decreasing the risk of COVID-19 infection and reducing pressure on NHS services. Within the currently available DMT treatment range, oral options are limited, and people with relapsing MS would benefit from a further safe and effective oral alternative. Importantly, if approved, Ozanimod would be the only first-line oral treatment available to people with MS who have had one relapse in the previous two years and MRI evidence of disease activity, as defined by NHS England's treatment algorithm for MS DMTs. The current lack of an oral option for this "active RRMS" group represents a clear unmet clinical need.
3	**The importance of patient choice and a wide range of treatment options** Patient decisions on which DMT to take are determined by a variety of factors including eligibility, efficacy, side effects, the method and frequency of administration, and lifestyle factors. Each DMT carries with it different levels of efficacy and risk. The more effective treatments that are available, the greater the choice for patients and the greater the likelihood that individuals will find a DMT that works for them. The patient expert stated: *"I think the thing for me is that it's really important there is a suite of medicines available as folk with MS are so very different. This can be different in how their MS manifests itself, what medicines are effective for them, what side effects they might get, their thinking on risk/benefit, whether they can cope with or undertake injecting etc. So I would like to see as many choices as possible. Also, MS folk tend to have to take different*

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	medicines as their condition changes, so again we need a suite of medicines available reflecting this journey MS folk are often on".
4	**The importance of a good safety profile** People with MS can face difficult and even frightening choices when they come to consider the risks and benefits of the different interventions for their condition. The patient expert summed this up in her request that the NICE committee "*do not underestimate the tough decision patients have to make when weighing up the risk profile of some of the medicines for MS".* She noted that some existing treatments for MS had serious side effects, meaning she had been unable to tolerate them, or, had chosen not to receive them. Considering that many people with relapsing MS may need to switch to an alternative DMT during the course of their disease, there remains a need for novel effective DMTs with a good safety profile. Clinical trial data has shown that ozanimod is reasonably safe and well-tolerated, with a similar safety profile to its Phase III trial comparator, interferon beta-1a. Ozanimod is a modulator of the sphingosine-1-phosphate receptor-1 pathway, as is fingolimod, an existing DMT in the standard treatment of relapsing MS. Fingolimod acts on four S1PR receptor subtypes, whereas ozanimod is selective to two. An indirect comparison of existing trial data showed that the two treatments appear to have similar efficacy, yet ozanimod demonstrated a more favourable safety profile with a lower risk of cardiac conduction abnormalities, slowing of heart rate and blood pressure changes, adding to the justification for the addition of ozanimod to the therapeutic arsenal for MS.
5	
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):	Multiple Sclerosis Trust
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Example 1	We are concerned that this recommendation may imply that ……..
1 General comment	The MS Trust is extremely disappointed that NICE is unable to recommend ozanimod as an NHS treatment for active relapsing remitting MS. We note that the committee recognises that ozanimod reduces the number of relapses and brain lesions compared with beta interferon and notes that ozanimod's effect on progression of disability is unclear. The committee has requested further analyses, reflecting their preferred assumptions. We trust that the manufacturer will provide these and respond to the technical issues raised. The difficulty in calculating cost effectiveness of MS drugs is well recognised.
2 General comment	**Ozanimod would be a valuable additional oral treatment** Ozanimod would be a valuable alternative to the two oral treatments currently used for active relapsing remitting MS: dimethyl fumarate and teriflunomide. Ozanimod has several advantages over these two treatments. **Dimethyl fumarate:** • Requires twice daily administration. Twice daily administration is associated with lower adherence[1]. • Adverse events The two most frequent adverse events for dimethyl fumarate are gastrointestinal problems and flushing. Gastrointestinal problems include nausea, vomiting, diarrhoea, and upper and lower abdominal pain. Discontinuation of dimethyl fumarate due to gastrointestinal adverse events has been relatively low in clinical trials (4% for dimethyl fumarate, <1% for placebo) but gastrointestinal adverse events have had a greater impact in clinical practice. For example, in one study, out of 100 patients prescribed dimethyl fumarate, there was an overall discontinuation rate of 13% with 9% discontinuing because of gastrointestinal tolerability issues, within the first 6 months[2]. While several strategies can reduce gastrointestinal adverse events and discontinuation[3,4], these place considerable additional demands on NHS resources, particularly MS specialist nurses and add to the burden of treatment for patients. Ozanimod does not cause gastrointestinal problems and would be welcomed by clinicians and patients as an alternative for those who have pre-existing gastrointestinal conditions or would reject treatment with dimethyl fumarate because of anticipated side effects. **Teriflunomide:** • **Lower efficacy** Teriflunomide is widely viewed as having lower efficacy against annualised relapse rate compared to dimethyl fumarate. In a real-world comparison of dimethyl fumarate and teriflunomide, teriflunomide

[1] Coleman CI, et al. Dosing frequency and medication adherence in chronic disease. J Manag Care Pharm. 2012 Sep;18(7):527-39.
[2] Allan M, et al. A Retrospective Analysis of Real-World Discontinuation Rates with Delayed-Release Dimethyl Fumarate in Patients with Relapsing-Remitting Multiple Sclerosis. Neurol Ther. 2020 Jun;9(1):85-92.
[3]Campbell TL, et al. Nursing Management of Gastrointestinal Adverse Events Associated With Delayed-Release Dimethyl Fumarate: A Global Delphi Approach. J Neurosci Nurs. 2020 Apr;52(2):72-77.
[4] Theodore Phillips J, et al. Consensus Management of Gastrointestinal Events Associated with Delayed-Release Dimethyl Fumarate: A Delphi Study. Neurol Ther. 2015 Dec;4(2):137-46.

	was associated with a higher relapse rate and higher discontinuation rate due to disease breakthrough[5]. The NMA indicates that ozanimod is more effective than teriflunomide against annualised relapse rate. • **Adverse events** Treatment with teriflunomide can cause nausea and diarrhoea. It also causes hair thinning and loss which is a significant concern for some patients. • **Risk of birth defects** Teriflunomide may cause serious birth defects and is contraindicated in pregnancy. Women must use effective contraception during treatment and after treatment as long as plasma concentration is above 0.02 mg/l. Teriflunomide plasma levels remain above 0.02 mg/l for 8 months, but in some patients this can take up to 2 years from stopping treatment. Because of this there is an increased risk of exposure to teriflunomide during pregnancy which continues for up to 2 years after stopping treatment. This is understandably a cause of concern for women considering a disease modifying treatment. Our own research shows that teriflunomide is one of the least prescribed of the disease modifying drugs[6]. A combination of lower efficacy, concerns about side effect and long elimination times are likely to contribute to reluctance of clinicians to prescribe and patients to choose this treatment.
3 3.5	**Disability progression** **We urge the committee to consider the results for disability progression in the context of previous NICE appraisals for disease modifying treatments.** A review of NICE FADs (see below) shows that in previous appraisals, the majority of disease modifying treatments have been shown to significantly reduce disability progression compared to placebo but not compared to active comparator. The committee notes that ozanimod's effects on disability progression are uncertain. Ozanimod was more effective at reducing relapses and MRI outcomes compared to interferon beta-1a. However, there was no statistically significant difference for CDP-3M or CDP-6M. Clinical experts considered that a treatment that reduced MRI activity and relapses would also be expected to reduce CDP. They considered that the people enrolled in RADIANCE part B and SUNBEAM may have milder relapsing–remitting multiple sclerosis than average and would be less likely to progress in terms of disability over the short duration of the trials. The CDP results were based on pooled data from RADIANCE (2 year study) and SUNBEAM (1 year study). The short duration of these clinical trials, particularly SUNBEAM, limit the ability to determine long-term effects on disability progression, particularly CDP-6M. The DAYBREAK open-label extension study will provide results when all patients have been exposed to treatment for a minimum of 5 years. **Disability progression discussed in previous NICE appraisals:** **Fingolimod TA254** https://www.nice.org.uk/guidance/ta254/chapter/4-Consideration-of-the-evidence 4.7 The Committee concluded that the available evidence shows that people with relapsing–

[5] Buron MD, et al. Comparative effectiveness of teriflunomide and dimethyl fumarate: A nationwide cohort study. Neurology. 2019 Apr 16;92(16):e1811-e1820.
[6] MS Trust. Evidence for MS specialists: findings from GEMSS. Letchworth: MS Trust; 2016

	remitting multiple sclerosis who are treated with fingolimod have lower relapse rates than people treated with Avonex or placebo. The Committee also agreed that fingolimod was shown to reduce disability progression in people with relapsing–remitting multiple sclerosis compared with placebo in the whole population of the FREEDOMS trial; however, there was no significant impact on disability progression compared with Avonex in the TRANSFORMS trial. **Beta interferons/glatiramer acetate TA527 2018** https://www.nice.org.uk/guidance/ta527/chapter/3-Committee-discussion 3.10 the treatments delayed disability compared with placebo but did not differ statistically significantly from each other. The committee concluded that the beta interferons and glatiramer acetate had similar effectiveness, and that they all delayed disability progression when compared with placebo. 3.13 The committee concluded that, consistent with the data from trials considered in the assessment group's network meta-analysis, all the technologies offered in the RSS delayed disease progression compared with best supportive care. **Dimethyl fumarate TA320** https://www.nice.org.uk/guidance/ta320/chapter/4-Consideration-of-the-evidence 4.11 The Committee concluded that, compared with beta interferons and glatiramer acetate, dimethyl fumarate is more effective in reducing relapse rates and as effective for disability progression. **Teriflunomide TA303** https://www.nice.org.uk/guidance/ta303/chapter/4-Consideration-of-the-evidence 4.5 The Committee agreed …. the proportion of people who experienced 3-month sustained accumulation of disability (SAD) was reduced with teriflunomide compared with placebo and that this difference was statistically significant in the TEMSO trial and in the meta-analysis (see section 3.4). The Committee agreed, however, that there was no statistically significant difference between teriflunomide and placebo in 6-month SAD in either of the placebo-controlled trials (see section 3.4). The Committee was aware that, although a statistically significant improvement in 3-month sustained accumulation of disability (SAD) was seen with teriflunomide, this was not seen for 6-month SAD. The Committee concluded that teriflunomide may have a beneficial impact on accumulation of disability. **Ocrelizumab TA533** https://www.nice.org.uk/guidance/ta533/chapter/3-Committee-discussion 3.7 It also noted that fewer patients had confirmed disability progression at 3 months and 6 months for ocrelizumab compared with interferon beta-1a, and that the difference was statistically significant (see table 1). The committee concluded that ocrelizumab reduces relapses and slows disability progression compared with interferon beta-1a. 3.11 The committee concluded that ocrelizumab slowed disability progression in the whole relapsing–remitting multiple sclerosis population compared with interferon beta-1a, interferon beta-1b, glatiramer acetate and teriflunomide, but not compared with some other treatments.
4 General	**Mechanism of action** Ozanimod belongs to the same group of drugs as fingolimod, a treatment which has shown to be very effective at reducing relapses and disability progression. Fingolimod is only available as a second line treatment, for people who continue to have relapses after taking a beta interferon. Ozanimod is more selective than fingolimod for the target subtype 1 of sphingosine 1-phosphate receptors which are expressed on lymphocytes and lead to sequestration of lymphocytes in lymph nodes. As a result, ozanimod might be expected to cause fewer side effects compared to fingolimod. In ozanimod clinical trials, first-dose monitoring showed no slowing of heart rate, liver enzyme levels increases were transient, generally resolved and did not lead to treatment discontinuation, and risk of macular oedema appears to be very low.

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	Approval of ozanimod would allow clinicians and patients to access this proven, very effective mechanism of action as a first line treatment.
5 General	**Conclusion** Ozanimod would be a valuable additional treatment for active relapsing remitting MS. Once daily oral route of administration means that ozanimod can be taken at home, eliminating potential delays in starting treatment which has occurred with other DMDs which require access to outpatient infusion clinics. Overall, this route of administration minimises demands on NHS services. Given the heterogeneous nature of MS, both in disease course and in response to treatments, a broadening range of drugs which work in different ways increases the potential for personalisation of treatment.
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):	Multiple Sclerosis Advisory Group as part of the Association of British Neurologists (ABN)
Disclosure 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	Firstly, on behalf of the Multiple Sclerosis (MS) Advisory Group of the Association of British Neurologists we are disappointed that Ozanimod was not approved in its recent NICE Technical Appraisal. The assessment was extremely thorough and raised several relevant issues which are noted in the NICE document. However, as the body representing clinicians treating MS, we are concerned that a potentially effective and well tolerated oral therapy which would have a place particularly in first line treatment of people with MS will not be reimbursed and available to clinicians and patients. We understand the concerns raised in the NICE appraisal but wish to provide the following additional information in the points below to provide important context in its likely practical clinical use.
2	**Positioning of the drug as a first line treatment vs second line treatment.** The separation of highly active MS and active MS (based on the number of relapses in the last year) and accordingly the classification of drugs suitable for each group is artificial and does not reflect the natural history of MS or take into account other clinical factors such as MRI activity. We would consider Ozanimod as predominantly a first line drug, useful for drug naïve patients, or those who switch from other treatments due to tolerability issues. However, there is a continuum of disease severity, with patients who would benefit from a more efficacious drug following a relapse, but in whom the risks of the currently available second line drugs may be deemed excessive by the patient or clinician. Fingolimod, which is an approved S1P inhibitor, currently fills this role, but has cardiac side effects necessitating cardiac monitoring for first dose or after treatment pauses of 2 weeks, unlike Ozanimod. Classifying eligibility for particular treatments according to the number of relapses in the last 12

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	months can create anomalies. Patients chose between the licenced drugs for many individual reasons and many prefer an oral medication with good tolerability over more potent which may have more long-term complications, even if they have had 2 relapses in the preceding year. It is reasonable to propose that a drug, predominantly used as a first line treatment, may be a useful second line treatment for many patients with intermediate disease severity.
3	**Highly active disease 'often defined as disease that has inadequately responded to disease modifying therapy'.** In practice this includes a wide spectrum of patients, some with a relapse after several years of stability on a first line drug, others with multiple relapses on a highly active treatment. Not all of these patients would be clinically suitable for all second line drugs, and Ozanimod, as a well-tolerated and safe drug would have a role in patients with moderate disease activity. The NHSE algorithm already distinguishes between second line drugs for this group of patients – NHSE requires evidence of new MRI activity for patients to be eligible for Cladribine and Natalizumab, but not for Ocrelizumab or fingolimod. There is a significant group of patients with clinical relapses without demonstrable MRI change and Ozanimod would be a useful alternative in this group, with a better side effect profile.
4	**It is not appropriate to limit the population for whom an oral treatment is suitable or who request an oral treatment.** This is not a clinician–defined category but is very important for many patients. Patients may need to switch from injections or other oral treatment due to intolerance or abnormal safety monitoring tests. For this group, another oral treatment, with a good safety profile, of similar or greater efficacy, would be of significant benefit.
5	**The committee conclude that all first and second-line treatments used for active relapsing-remitting MS, including Ocrelizumab, were comparators.** Ocrelizumab is the currently the only drug on the NHS algorithm which is approved for patients in all stages of the disease – from a single clinical event, through active to highly active or rapidly evolving severe MS. It is not the most suitable drug for all patients with MS, given the potential long term immunological issues, and of particular concern now, likely reduction in response to Covid vaccination or more severe infection. Using Ocrelizumab as a comparator for all other treatments, whatever their potency and safety profile, does not take account of the clinical and patient choice factors involved in drug selection.
6	**Ozanimod reduces relapses and brain lesions compared to interferon beta-1a but its effects on disability progression are uncertain.** Radiance had a 24-month follow-up period, Sunbeam had a 12-month follow up period, mean time to progression of disability in untreated patients is 10 years. Both trials recruited patients with relatively mild (mean EDSS 2.5), early (mean duration since diagnosis 3.2 years) disease. Reduction in both relapse frequency and accumulation of MRI brain lesions is very likely to translate to reduced disability over many years, not captured in short clinical trials. Other MS disease modifying drugs approved by NICE could not demonstrate reduction in disability at 6 months compared to interferon but are considered in clinical practice to be superior. It seems unlikely that interferon has a greater real-life effect on clinical disability than Ozanimod, given the relapse and MRI data, and therefore using the CDP-6M data from the trial (which does not capture longer term benefits) may give an artificially low estimate of cost-effectiveness. The high quality of the trials commented on in the report as a reason to use this data, cannot overcome the inherent problem of attempting to measure long-term outcomes in a 12- or 24-month trial.
7	**Modelling of treatment discontinuation.** A significant cause of treatment change in clinical practice is lack of drug tolerability – and the Ozanimod trials show low rates of significant side effects.

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Novartis Pharmaceuticals UK Ltd
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

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1	**Novartis supports the Committee conclusions on treatment pathway, population and comparators** Novartis firmly agrees with the Committee conclusions on the likely use of ozanimod as a further option for first- or second-line treatment of active RRMS, if recommended. As such, Novartis also firmly agrees that all DMTs currently available in NHS England for first-and second-line treatment of RRMS are relevant comparators in their respective positions, including ocrelizumab.
2	**Novartis supports the Committee preference for CDP-6M; it is not appropriate to use CDP-3M data when CDP-6M data are missing** Novartis welcomes the Committee preference for use of CDP-6M data wherever available. In cases were CDP-6M data are not available, Novartis contends that CDP-3M data ought not to be used in their place, nor should any attempt to infer a CDP-6M result from a CDP-3M result be made. Novartis acknowledges that excluding CDP-3M data entirely would result in exclusion of Rebif® 22 (interferon beta-1a 22µg) and peginterferon beta-1a from the NMA considered in this appraisal and thus from the economic results, but contends that this is not a barrier to decision making in practice: Rebif® 22 is a step-down dose for patients who cannot tolerate the standard Rebif® 44 dose (for which CDP-6M data are available) rather than a distinct comparator, while the peginterferon beta-1a trial has been excluded from the NMA as an outlier by the Committee in a previous appraisal (TA533). With respect to the Committee considering a secondary NMA wherein CDP-3M data are used to impute missing CDP-6M data, Novartis contends that the attempt to incorporate CDP-3M into an NMA focussed on CDP-6M is methodologically unsound. The reason that CDP-6M is preferred by the Committee for decision-making in this and other recent previous MS appraisals (e.g. TA533) is because CDP-3M may be confounded by the residual effect of relapses, and the effect of this residual confounding on the direction of the relationship between CDP-3M and CDP-6M in any given trial is random and variable: attempting to infer a relationship from these data is inherently unsound as no trial can provide evidence for the direction of the relationship in any other trial. This point is exemplified by the fact that in the two pivotal trials for dimethyl fumarate, DEFINE and CONFIRM, the direction of the relationship between CDP-3M and CDP-6M differs: in the DEFINE trial the hazard ratio for CDP-3M is 0.62, and for CDP-6M is 0.77, whereas in the CONFIRM trial the hazard ratio for CDP-3M 0.79, HR for CDP-6M 0.62 (hazard ratios are dimethyl fumarate vs placebo, data are quoted from paragraph 3.5 of NICE TA320). Novartis therefore requests that decision-making ICERs are not generated from any analyses incorporating CDP-3M data.

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3	**The approach to modelling treatment discontinuation should align with previous appraisals** As the clinical experts stated, it is acknowledged that people with RRMS are likely to be treated with a number of DMTs over time. However, as noted in the Novartis response to Technical Engagement in this appraisal, the sequence of treatments is highly individualised and capturing all permutations would be hugely complex and require many assumptions, risking the decision-making ICERs being driven by the choice of assumptions regarding sequencing, rather than by the available data. While the company approach of disregarding sequencing is criticised in the ACD, it would appear to have been accepted as the pragmatic option. This aligns with past appraisals and Novartis welcomes this preference and continues to disagree with the ERG proposals on this issue.
4	**Inclusion of arbitrary waning assumption is inappropriate and biases the ICERs in favour of ozanimod** The ACD states (paragraph 3.7) that the company model "incorporated a treatment waning effect for all treatments" yet the ACD also states (in the bold heading text above paragraph 3.7) that the model "aligns with previous models in the disease area". This statement ("aligns with…") is inaccurate with respect to waning: the Committee has not preferred to include waning in all previous appraisals and, in those appraisals where it has preferred to include waning, the level and timing of waning onset has varied considerably. The inclusion of waning is not aligned to the Committee conclusions in TA533 where all-cause treatment discontinuation was considered a proxy for any waning. In addition, the waning assumptions used by the Company are not aligned with TA527, for example, where waning was not applied until after ten years of treatment (as opposed to after two years for all DMTs in the model in this appraisal). Novartis is not aware that any evidence has been presented in this appraisal to support the application of waning to any DMTs and, as such, waning represents an arbitrary bias in the model. Importantly, Novartis requests that the Committee explicitly addresses the fact that the effect of the Company waning assumptions combined with the Committee preference for using the ozanimod CDP-6M value from the NMA will be to bias the ICERs in favour of ozanimod and against all other DMTs because the Company Submission states (Section B.3.3.7.1.2, page 94) that waning is not applied where the hazard ratio versus placebo is above one, as is the case for the Committee preferred hazard ratio for ozanimod. It should be noted that even if the Committee were to prefer a value for this hazard ratio below one, it may still bias the ICERs against all comparator DMTs which are modelled to have greater efficacy than ozanimod because the arbitrary waning assumption is applied as a percentage and therefore more effective DMTs incur a greater absolute loss of effect than less effective DMTs. Novartis therefore requests that waning be removed from the decision-making ICERs, in alignment with the Committee preferences for TA533.

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5	**Request for clarification of wording in any future ACD, FAD or Technology Appraisal Guidance** The ACD states in paragraph 3.1 (page 5) "Ozanimod is also an S1PR modulator and does not have the same cardiac side effects as fingolimod." Novartis, as the manufacturer of fingolimod, requests that the above phrase be changed to "Ozanimod is also an S1PR modulator, with its own distinct cardiac safety profile". Novartis understands that what was referred to during the appraisal committee meeting was the requirement for all patients to undergo first dose cardiac monitoring when initiating fingolimod and the known cardiac side effect profile of fingolimod. Novartis notes that the ozanimod summary of product characteristics requires first dose cardiac monitoring for patients with certain pre-existing cardiac conditions, and that, in Table 2 of the ozanimod summary of product characteristics, cardiac adverse events are stated to be "common". Novartis is concerned that the ACD text could be incorrectly interpreted as stating that ozanimod has no cardiac side effects.

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Patient Expert MS Society
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**
Name of commentator person completing form:	Lorraine Hazlehurst

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	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 would like to stress the need to ensure there is a suite of medicines for MS. The individual nature of this condition means that patients will have a different needs, experiences and capability. This will impact their ability to administer their medicine, whether they can tolerate the side effects and what risk/ benefit they feel is appropriate to them. Also, medicines work for some but not all and many patients may have to take a number of medicines before they find the one that makes a difference to them - and this is likely to change throughout their health journey.
2	I think there could be a greater emphasis on the improved side effect profile for this medicine.
3	I would like add more emphasis on the impact of this being an oral medicine and the benefit this gives the patient (ease to take and its potential to improve compliance, taking the pressure and stress out of taking the medicine)
4	
5	
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):	**Eli Silber, Consultant neurologist, expert witness**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**I was a trialist in one of the Ozanimod studies, nil else**
Name of commentator person completing form:	**Eli Silber**

Comment number	**Comments** Insert each comment in a new row.

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	Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	**Why the committee made these recommendations:** I am concerned about the sentence "It is uncertain how effective ozanimod is compared with other treatments as there is no evidence directly comparing them". I am concerned that this drug is expected to meet different standards to other disease modifying therapies. All studies have either compared the drug to placebo or to an established first line therapy, usually an interferon drug as in the case of ozanimod. Efficacy compared to other therapies has usually been extrapolated by comparing rates in the different trials, as in this case.
2	**Paragraph 3.1** This deals with positioning of the drug. Both experts emphasised that there is considerable overlap and clinical judgment in classification of patients with relapsing-remitting MS and that supported its potential use in treatment naïve patients "first-line therapy" where in contrast to other oral therapies it is licensed in patients who have had only one attack in the last two years. We also supported this being an alternative to fingolimod in patients with possible cardiac concerns. This did not include patients with so called RES disease.
3	**Paragraph 3.3** I agree that a broad range of comparators, including ocrelizumab be included. However, it must be emphasised that in general, drugs with greater efficacy are likely to have greater risks of side effects (there are recent concerns about hypogammaglobulinemia in the anti-CD-20 monoclonals) and that whilst patients may be offered a range, they may choose to restrict their decisions based on their own perceived risk profile.
4	**Paragraph 3.4** It is notable that the patient characteristics of trial subjects suggest a relatively mild disease course in general. Only 30% had a prior DMT and 23% could be classified as having more active forms of the disease. This may explain the low CDP described.
5	**Paragraph 3.5** Regarding the effects on CDP, although the rates of CDP were lower in the Ozanimod than in the interferon group in both trials these differences were not statistically significant. It was suggested that the a. low levels of disease activity and b. short trial duration were the major contributors to this. Given the effects on relapses and MRI activity I would expect a significant effect on CDP over a longer period.
6	**Paragraph 3.8** I am concerned at any suggestion that ozanimod may not work as well as interferon for CDP. The data suggest superiority, rather than inferiority for ozanimod but in this study these did not reach significance.
7	**Paragraph 3.9** Regarding treatment switching, we had emphasised that both models do not accurately reflect clinical practice. I would want to be sure that these models are treated consistently in all of the recent MS DMT applications and that this drug is not required to meet more (or less) stringent standards than other therapies.

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 links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with

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[Ozanimod for RR MS]

Consultation on the appraisal consultation document – deadline for comments 5pm on [insert consultation deadline] **email:** NICE DOCS

the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.

- 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 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 appraisal consultation 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.

Comments on the ACD received from the public through the NICE Website

Name	[redacted]
Role	
Other role	
Organisation	Barts Health NHS Trust
Location	
Conflict	
Notes	
Comments on the ACD:	
Has all of the relevant evidence been taken into account?	
Yes	
Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?	
The place of ozanimod will be in line with the dimethyl fumarate and it should be modelled as such. The comparison with beta interferon is not complete.	
Are the recommendations sound and a suitable basis for guidance to the NHS?	
No - the place of comparison is not correct.	
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?	
MS is a disabiling condition and so by limiting patient choice it is increasing inequalities amongst this disadvantaged group.	

ERG comment on the company response to the ACD

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Ozanimod for treating relapsing–remitting multiple sclerosis

ERG comment on the company response to the ACD

Confidential until published

This report was commissioned by the NIHR HTA Programme as project number NIHR 17/156/08

Completed 15 March 2021

UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

1 INTRODUCTION

The ERG has been invited to comment on the company's response to the ACD.

2 ERG COMMENT

As the company has correctly pointed out, it is stated in the January 2020 ERG report that only statistically significant differences between treatments should be modelled. However, in part, due to our recent collaborative work on the development of DSU guidelines on non-inferiority testing and cost minimisation analysis, the ERG's views have changed. The ERG now considers that overlapping or wide confidence intervals are not sufficient to conclude that there is no difference in effectiveness between treatments, and that the similarity of treatments needs to be robustly demonstrated using pharmacological and statistical evidence before it is appropriate to only consider differences in terms of costs.

In this appraisal, the ERG considers that there is insufficient evidence to conclude that the effectiveness of treatment with ozanimod and the comparators is similar for the following reasons:

- Ozanimod has a different mechanism of action to the relevant first-line comparator treatments.
- When compared to all the relevant first-line comparators included in the NICE scope (company's original NMA networks):
    - Ocrelizumab is statistically significantly superior to ozanimod for both ARR and CDP-6M
    - For ARR, while ozanimod is statistically significantly superior to all but two of the other relevant comparators, one of the two exceptions is DMF. Based on clinical advice received, the ERG considers DMF to be the main comparator to ozanimod
    - Ozanimod is not statistically significantly superior to any of the comparators for CDP-6M.
- When compared to only DMF and teriflunomide (company's reduced NMA networks):
    - Ozanimod is not statistically significantly superior to either DMF or teriflunomide for ARR or CDP-6M
    - For ARR, evidence suggests that ozanimod is non-inferior to teriflunomide, but there is insufficient data available to demonstrate that ozanimod is non-inferior to DMF
    - There is insufficient data available to demonstrate that ozanimod is non-inferior to either DMF or teriflunomide for CDP-6M.

The ERG, therefore, considers that it is not appropriate to only consider cost differences.