NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Ponesimod for treating relapsing multiple sclerosis [ID1393]

Committee Papers

NICE National Institute for Health and Care Excellence

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Ponesimod for treating relapsing multiple sclerosis [ID1393]

Contents:

The following documents are made available to consultees and commentators:

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

Ponesimod for treating relapsing multiple sclerosis [ID1393]

Single Technology Appraisal

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Type of stakeholder:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and Social Care and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD, if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal document (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation.

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health and Social Care, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful, or publication would be otherwise inappropriate.

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

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
1	Commentator	Merck Serono Ltd	Merck Serono Ltd (Merck) noted Section 3.9 of the Appraisal Consultation Document (ACD): *"The committee noted that cladribine had a substantially higher treatment effect for 6-month confirmed disability accumulation than other treatments in the network meta-analysis for the highly active subgroup (see section 3.7). It noted that this estimate had wide credible intervals, indicating a high level of uncertainty. The committee noted that because 6-month confirmed disability accumulation is a key driver of the model (see section 3.12), this estimate also had a large impact on the cost-effectiveness estimate of cladribine. The clinical experts did not consider that cladribine shows a substantially greater treatment effect than other comparators in clinical practice, which is supported by results from the full population analysis. The committee considered that this anomalous result needs exploring further, particularly if there were any characteristics from the cladribine trials which could explain this."* As the manufacturer of Cladribine Tablets, Merck would like to respond to this section of the ACD. Firstly, we acknowledge that the redactions in the company submission and other relevant documents mean that we cannot comment on the specific NMA results described for Cladribine Tablets. Secondly, we wanted to highlight that there is no detail provided on the questions asked to clinical experts about Cladribine Tablets, so it is hard to comment on the specific opinions given here. Further detail on how this expert opinion was obtained would be valuable to support interpretation of this section. In response, Merck would like to provide analysis/data for Cladribine Tablets to support the efficacy in the relevant RRMS subpopulations. Specifically, this will cover: A. The highly active disease (HAD) subgroup as defined by NICE: Patients whose disease progressed or remained unchanged within the last year despite having previous disease modifying treatment B. The broader HAD subgroup, in line with similar definitions from the ponesimod clinical trial (OPTIMUM) and in line with the Cladribine Tablets marketing authorisation[1]: Patients with ≥2 relapses in the year prior to study entry whether receiving a disease modifying therapy (DMT) or not; and patients with ≥1 relapse during the year prior to study entry while receiving a DMT with ≥1 T1 gadolinium-enhancing or ≥9 T2 lesions o This definition of highly active RRMS is broader than the NICE definition, and thus also incorporates patients with rapidly evolving severe (RES) RRMS as defined by NICE. o This subgroup is also relevant for this response, as in the NMA provided in the company submission, trials were selected for inclusion in the analysis based on their alignment with the definition used in the OPTIMUM trial. As described in the	Thank you for your comments. The reliability of the available evidence is considered by the Committee when formulating its recommendations. See section 3.9 of the FAD for conclusions relating to cladribine. Recommendations are based on evidence of both clinical and cost effectiveness.

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			company submission: "*For all three efficacy outcomes, it was found that a network containing all relevant comparators would not be possible, due to a lack of reported subgroup data for some outcomes. To ensure full network connectivity, an assumption was made that the outcomes for the ITT population were equivalent to those of the HAD RRMS subgroup in these trials, similar to analyses presented in TA533*." In TA533 the committee concluded that this assumption led to uncertainty in the clinical effectiveness of ocrelizumab versus comparators in the HAD and RES subgroups. Merck would also like to clarify the distinction between the two definitions of HAD. The ponesimod ACD, and the discussion about the efficacy of Cladribine Tablets in this ACD, refers to the narrower NICE definition of HAD as stated in point A above. However, the marketing authorisation for Cladribine Tablets corresponds to the broader HAD subgroup, as defined in point B above.[1] This broader definition is also aligned to the NICE recommendation for Cladribine Tablets, as it also includes the RES subgroup (TA616). Brief summaries of the published studies demonstrating efficacy of Cladribine Tablets are provided below: **Giovannoni et. al. 2019. Efficacy of Cladribine Tablets in high disease activity subgroups of patients with relapsing multiple sclerosis: A post hoc analysis of the CLARITY study[2]** The efficacy of Cladribine Tablets in the broader HAD subgroup was reported in Giovannoni et al.,[2] which was a post hoc analysis of the pivotal CLARITY Phase 3 study. Outcomes of patients randomised to Cladribine Tablets 3.5 mg/kg (n=140), or placebo (n=149) were analysed for the definition described above in the broader HAD subgroup. Cladribine Tablets reduced the risk of 6-month-confirmed CDP by 82% (risk ratio: 0.38 [95% CI: 0.07-0.43; p=0.0001]), and 95.5% of patients were free from 6-month CDP with Cladribine Tablets, compared to 77.7% with placebo.[3] NEDA-3 (no evidence of disease activity; defined no relapses, no 6-month sustained change in EDSS and no new T1 gadolinium-enhancing lesions or active T2-weighted lesions) was also achieved in 44% of patients with HAD who received Cladribine Tablets compared to 9% with placebo, and 77% were relapse free, compared to 50% with placebo.[2] This analysis demonstrates that patients identified within the broader HAD criteria showed clinical and MRI responses to Cladribine Tablets, in a group of who may be at risk of poor long-term clinical outcomes. **Berardi et al. 2019. Estimating the comparative efficacy of cladribine tablets versus alternative disease modifying treatments in active relapsing–remitting multiple sclerosis: adjusting for patient characteristics using meta-regression and matching-adjusted indirect treatment comparison approaches[4]** This publication reported on the methodology and results of a study which estimated the comparative efficacy of Cladribine Tablets versus alternative DMTs – fingolimod, natalizumab, alemtuzumab and ocrelizumab – in adults with active RRMS subgroups, using meta-regression to provide sub-population specific estimates of drug effect. Of note, this study provided results for the broader HAD definition (in line with Giovannoni et al.[2] and with previous clinical trials, including OPTIMUM), as well as in the specific HAD population defined by NICE. In this publication, the NICE definition of highly active disease was referred to as the sub-optimal therapy (SOT) subgroup. A Bayesian meta-regression analysis was conducted to provide HAD-, RES- and SOT-specific estimates of the relative	

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			effect of Cladribine Tablets compared to the relevant DMT comparators. The focus of the publication is on the key highly efficacious comparators of alemtuzumab, natalizumab, fingolimod and ocrelizumab. The comparative effectiveness data was generated by running a series of models with adjustment for baseline risk that were fitted to data from the ITT cohorts of trials identified in a systematic literature review (SLR). The analysis was based on methodology for meta-regression on baseline risk published by the NICE Decision Support Unit. More detail on the methodology can be found in the study publication and supplementary appendix.[4] The results of the meta-regression analysis showed significant overlap in the credible intervals for the hazard ratios (HRs) of 6M-CDP, with no therapy statistically dominating in terms of efficacy. At the point estimate level, Cladribine Tablets were predicted to be more efficacious in the broad HAD population than fingolimod (HR: 0.77, 95% CrI [0.40; 1. 44]), alemtuzumab (HR: 0.92, 95% CrI [0.40; 2.23]) and ocrelizumab (HR: 0.87, 95% CrI [0.36; 2.02]). However, a similar result was not found for the comparison of Cladribine Tablets and natalizumab (HR: 1.08, 95% CrI [0.53; 2.21]). In general, similar trends were seen for SOT and RES subpopulations. Consequently, the results of these meta-regression analyses suggest that Cladribine Tablets have comparable efficacy to alternative high-efficacy DMTs in active RRMS, specifically in patients diagnosed with HAD, RES or SOT. These findings also support previous network meta-analysis that suggested Cladribine Tablets were a comparatively effective and safe alternative to other DMTs in RRMS patients with high disease activity. Note, ponesimod was not included in this comparison. In conclusion, this rigorous analysis confirms a need to adjust for population characteristics when estimating relative treatment effects in RRMS to account for the heterogeneity across clinical trials, particularly when these are used to re-estimate absolute treatment effects (such as in health economic analyses), as the resulting effect sizes can differ across sub-populations. The ponesimod ACD notes that the ponesimod NMA used unadjusted effects from each of the included trials, and the company did not calculate effects using meta-regression: in effect, therefore, the company have assumed homogeneity in the trial evidence, despite evidence that this is not the case. As noted in the ACD, this makes the results from the company's network meta-analyses highly uncertain and therefore should be interpreted with extreme caution. Merck believe the data provided above support the clinical efficacy of Cladribine Tablets in the broad HAD and NICE-defined HAD (referred to as SOT in Berardi *et al*. 2019) subgroups. As noted above, the Berardi 2019 study showed that no therapy statistically dominated in terms of efficacy, however at the point estimate level Cladribine Tablets were more efficacious than most of the comparators. The result of Berardi 2019 could be interpreted to align with the clinical expert opinion in the ponesimod ACD, as clinicians did not consider that Cladribine Tablets showed a ***substantially greater*** treatment effect vs comparators, and superior efficacy of Cladribine Tablets in the Berardi 2019 study was not statistically significant. However, we cannot be certain as we are not able to review the exact NMA outputs due to redactions in the committee papers, and the lack of detail on the clinical expert opinion further prevents interpretation. The committee considered that this anomalous result needs exploring further. We have presented here the results of a separate published indirect treatment comparison (albeit without ponesimod included) which adjusted for population characteristics when estimating treatment effect. As such, we believe that it may be worth exploring the methodology of the company's NMA which led to this anomalous result, rather than the characteristics of CLARITY, given the lack of an anomalous result	

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			for Cladribine Tablets in an alternative indirect treatment comparison. Merck considers that without exploring the company NMA methodology further, it is unreasonable to comment on the efficacy of a particular comparator product and clinical trial characteristics. **References** 1. Cladribine Summary of Product Characteristics. 2. Giovannoni G et al. Mult Scler J. 2019; 25:819–87 3. Merck Data on file. CLAD009. 4. Berardi A et al. Curr Med Res Opin. 2019;35(8):1371–1378.	
2	Consultee	MS Society	**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. In general, the MS community are positive about the potential for a further oral treatment option, not only for its simplicity but also as a means of reducing the complications from regular injections. Not every person with MS is suitable for or will have a preference for an oral option, but people with MS often tell us of a preference for tablets. 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. One person with MS told us "*My DMT journey began with injections. Being diagnosed with MS was mind blowing and then on top of this I had to come to terms with injecting. It felt like a lot to deal with and honestly impacted my compliance to my medicines. After 2 injectable medicines failed to control my MS/impacted my liver, I was given an oral DMT. My level of compliance has significantly increased. It's much easier to take a capsule. When you are not feeling well, when days aren't bright then having to perform an injection seems intolerable. But I am able to take a capsule… when assessing new medicines being made available to people like me, please remember that the ease of taking them matters".* Another person with MS said " *An oral tablet would be easy for me to administer myself which wouldn't be possible if an injection were required. It would mean I could maintain some better quality of life with the chance of enjoying the things that make my life more enjoyable and manageable for longer. It would allow me to continue to live independently in my home without relying on carers which is a very scary thought for me."* Others agreed with this and explained why they would prefer an oral therapy: *"Knowing someone who has injected Avonex Interferon for many years I can say that injecting once a week takes its toll on mental wellbeing"* *"I have been using Rebif since 2008. I inject three times per week, and I have developed lesions in some injection site areas. I am concerned that I will no longer have sites in which to inject"* *"I would love a tablet instead of an injection that takes about 8 hours to do. "*	Thank you for your comment. The views of clinical experts and patient/carer representatives were considered by the Committee when formulating its recommendations. Ponesimod is now recommended in the FAD.

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			"Injecting was so difficult, to hold the needle, to aim for the right area, and then the general pain and irritation at the injection sites were nasty. I would've given anything to have tablets instead." *"Life revolved around the correct times to take the injection out the fridge, remember if it was injection day, inject correctly, and how I'd feel after. It was like clock watching! Going away anywhere involved taking the correct number of injections with me."* 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. A 2014 study (1) comparing hypothetical choices of oral versus other DMTs showed that oral options were preferred over injections by 93% of patients, when frequency of treatment use and of side effects were held to be constant, although preferences switched to injections if the oral options had to be taken three times daily and injections only once per week. Importantly, if approved, ponesimod 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 relapsing MS group represents a clear unmet clinical need. **References:** 1. Utz et al., 2014. Patient preferences for disease-modifying drugs in multiple sclerosis therapy: a choice-based conjoint analysis (nih.gov)	
3	Consultee	MS Society	**People with MS value choice in treatment options** Decisions on which DMT to use can be complicated and are determined by a wide range of factors including effectiveness, eligibility, the level of side effects, the method and frequency of administration, as well as individual lifestyle factors. Individual preferences and weight attached to different factors can be as variable as the condition itself. The wider the range of safe and effective treatments, the greater the choice for people with MS and the greater the chances than an individual will find a DMT that works for them. One person with MS told us- *"Deciding to take DMTs is often not a simple decision. It can require you to perform injecting yourself, it may require infusions in hospital, and it will definitely require you to weigh up the risk/benefit of the potential impact to your conditions journey vs the potential side effects.* *Effective treatments that are both easy to take and tolerate are very important to made available to patients. Dealing with MS means we have the physical impact to deal with, but we also have the mental toll to handle. Our medicines should not be part of this burden.* *Personally, I have declined certain DMTs because of the serious side effect risk even if they have*	Thank you for your comment. The views of clinical experts and patient/carer representatives were considered by the Committee when formulating its recommendations. Ponesimod is now recommended in the FAD.

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			good clinical profile because I can't risk anything else to deal with. *I think when assessing new medicines being made available to people like me, please remember that the ease of taking them and the ease of tolerating them matters."* In response to the news of NICE's initial decision on ponesimod, some people with MS wrote to us about the general need for more treatments, given how severe the condition can be. One person said "*Please don't stop any new medicine for MS- we need to try as many as we can. MS has robbed me of my life. I've had to stop work which I loved and driving. The lockdown was terrible, and I can't get out of house on my own. Walking is bad and painful. It's soul destroying. "*	
4	Consultee	MS Society	**Ponesimod was effective for people who were on the trial** In response to our news story about NICE's initial decision on ponesimod, the MS Society was contacted by six people with MS who have taken part in one of the clinical trials of this treatment. Strikingly, all of these people described what they saw as very good responses to the treatment and felt it should be approved. Some of these people wished NICE to be informed that they would be willing to provide any further information required for the appraisal. **Person A** "I have been on the medication since 2010. I had 6 relapses prior to enrolling on the study and have had none since. My EDSS score of disability was 1.5 at baseline in September 2010 and was 1.5 in September 2021, showing that I am in the same position. I have had no relapses in 12 years, further, any sensory and muscle related symptoms have disappeared. I feel cured. This is a remarkable drug and has given me freedom to live my life. I have had no days off sick for MS in 12 years. I work full-time, and I am a father of two boys. I walk, run, cycle and we're going skiing in February. If you wanted a walking advert for Ponvory, then it is me. I believe that the ability for Ponvory to effectively stop MS in its tracks, the ability to reverse symptoms, to prevent disability, and for patients to remain relapse free for many years is nothing short of amazing. It has the potential to transform people's lives. For the newly diagnosed it offers stability of the life they're living today, and for those with some level of disability, it offers hope that they won't get worse, and might actually improve. It should be the first line of defence offered to patients upon diagnosis." **Person B** I have heard today that the drug Ponesimod has been initially refused by NICE. I have been a participant in this drug trial since…2010 and wish to share my experience. I am very disappointed with this news.	Thank you for your comment. The views of clinical experts and patient/carer representatives were considered by the Committee when formulating its recommendations. Ponesimod is now recommended in the FAD.

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			I was diagnosed with RRMS at the age of 47 in 2010 and after 11 years of being on the drug, I understand I am according to my Consultant….“doing very well”. I lead a full and happy life and although I have some sensory issues and suffer from fatigue from time to time, I am fully mobile and my MS does not stop me doing anything that I wish to do. Ponesimod is a ground breaking drug that could help MANY people with RRMS and surely the opportunity cost of the saving in cost of the future health care of people with RRMS must be weighed against the cost of providing the drug that could make such an enormous difference to the lives of many. I have experienced no side effects and have found the ease of taking a tablet each day is helpful. Above all I have hope that although I understand that the progressive nature of this neurological condition makes it likely that I will slowly decline, I cling onto hope that I may not require a wheelchair in the future. I hold onto this hope and can honestly say hand on heart, that I believe Ponesimod has been the reason for my good health. What price does NICE place on the quality of life of someone with MS? What happens to the participants who have given up 11 years of their life for endless hospital appointments in the hope that they may make a difference to the lives of others with RRMS in the future? Where are the ethical considerations in this also and will we be able to continue on this drug? I await further information and am absolutely devastated with the news announced today” **Person C** “I have heard today that NICE does not recommend Ponesimod (Ponvory) as an NHS treatment in England and Wales....my personal experience has been exceptional. In the year before starting the drug I suffered drop foot, double vision, numbness on my face and severe fatigue. I started the drug a few months after my last relapse and haven’t had a relapse since… that’s 11 years!! Your argument against the drug is that you are ‘unsure of Ponesimod’s ability to slow down disability progression’ and therefore, ‘ponesimod is not considered to be cost-effective for the NHS’. This has been an 11 year trial and for me to have no relapses is incredible. I do not need to claim disability benefits because of the effectiveness of this drug. …I look to my future and obviously consider that my condition may worsen but hope that I; do not lose my voice, my mobility or my sight to name but a few devastating effects that this disease can bring. I truly believe that Ponesimod has been the reason for my continuing good health. What price does NICE place on the quality of life of someone with MS? Participants have selflessly for the last 11 years given their time for hundreds of hospital appointments in the hope that they may make a difference to the lives of others with RRMS in the future? Every bit of feedback I have had about this drug has been nothing but positive and I will	

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			be devastated if it isn't approved" **Person D** "I was very surprised and concerned to hear of NICE's recent decision about Ponesimod. As someone who has been taking this medication I thought that you may be interested to hear of my experience. I was diagnosed with MS early in 2010, and have been on the Ponesimod trial since August of that year. I had had three relapses, and my MRI showed in excess of 10 lesions. Since starting Ponesimod I have had no further relapses, and my recent MRI showed no new lesions compared to 2010. My fatigue levels are also exactly the same as they were 11 years ago. NICE are concerned about Ponesimod's effect on disability progression. In terms of disability, I would say that I am essentially unchanged from when I was diagnosed, and in some ways have actually improved - for example, I no longer get "foot drop" after walking for 20 minutes. I think that most people, even those who do not have MS, would not be able to say the same after 11 years. In addition to my personal experience, the others I have met on the trial all report similar outcomes" **Person E** "Before this medication I was having relapses approximately every three months. From losing my sight in one eye to being unable to walk for a periods of time due to numbness and loss of sensation, to name but a few adverse relapse conditions I've experienced since being diagnosed with MS This medication has been a godsend and has enabled me to build my own business and live my life to the full. Since being on this medication for over a decade now I cannot sincerely remember any time when I've had a MS relapse or any other adverse affect from the actual medication. I am able to work, provide for my family and contribute to society I do believe things would of all been different had I not been lucky enough to go on this trial Working in the city centre and dealing with hundreds of people every week none of them would think I had anything wrong with me which truly proves the effectiveness of the medication and if all people with MS were in my similar physical, mental and well-being state of health and mind then I think they would all want to be on the medication. Having seen the severe impact MS can have some people's health, well-being and quality of life I feel very fortunate." **Person F** "You will by now have been presented with all the scientific data about Ponesimod and have scrutinised all the facts and figures. I can add nothing to this; I can only offer an account of what Ponesimod means to me and how it has impacted on my life. I was initially diagnosed with MS in 2009/2010, first presenting in … 2009. … Luckily my consultant	

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			was involved in the clinical trial for Ponesimod that was about to commence and i was offered a place on it. I started on Ponesimod clinical trial in June 2010. I don't know if I was on the medication or placebo at the start of the trial - certainly, I had no relapses, although I continued to experience fatigue, some physical and cognitive distress. I was still consumed by the memory of that horrible episode, the fear of it recurring, of how my future could be impacted. Within a couple of years on the trial I began to realise that I was feeling increasingly stable. That I could begin to imagine a normal life for myself, a normal future. Ponesimod is so easy, so unobtrusive. Just a simple pill taken every day. As I was accepted on to the trial so soon after diagnosis, I have no experience of other drugs or treatments, so I cannot offer a comparison, but I can say that the simplicity and efficacy of Ponesimod has allowed me to get on with life without MS completely dominating it. No drips, no injections. Just one little pill and I'm good to go. I have had zero relapses, very few minor episodes, no work days lost, no impact on my daily life since being on this drug, and no side effects. My initial EDSS score was 1.5; it has since improved to a score of 1. I have experienced a return of sensations in digits that I had lost since the initial episode, and although I still experience intermittent symptoms such as spasms, these are increasingly rare and mercifully brief. I feel generally well in myself, in fact, I feel better than I did before my diagnosis, which suggests to me that I may have been suffering from MS for some time previous to my crisis. Sometimes I feel like a fraud when I say I have MS; you honestly wouldn't be able to tell. But every day I take my pill I offer a silent prayer of gratitude that I no longer experience what I never allow myself to forget: the pain, the fatigue, the mental confusion - but above all the fear. For my mobility, my employment, my independence, my personal relationships, my mental state. Those specific fears have now dissipated. Now my fears are of what will become of me if Ponesimod is no longer available to me. I know there are other treatments available, but this one is so effective. It has given me back the confidence to face the future and to imagine and plan for a normal life. I know it can do the same for others. I'm sure that you can see the science and evaluate how successful Ponesimod is in the treatment for relapsing MS, but what the data cannot tell you is how important it is for the mental and emotional wellbeing of us, the MS sufferers who have been fortunate enough to have had the opportunity to trial this drug”	
5	Consultee	MS Society	**The impact of effective MS treatment options on carers and wider society** The wide-ranging impact of MS, its progressive nature, the relatively young average age of onset and the many years people spend living with the disease all mean that any effective treatment has an large effect not only on individuals, but also on carers and at a societal level. It is difficult to capture this in standard cost benefit analysis. People with MS often need support from family and/or friends to help them manage the impact of	Thank you for your comment. The views of clinical experts and patient/carer representatives were considered by the Committee when formulating its recommendations. Ponesimod

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			having MS and help them maintain their independence. This includes support with everyday tasks like washing and dressing and getting out and about. As disability progresses the need for this support increases and the impact on carers can be greater. Our 2019 My MS My Needs survey (1) showed that 40% of respondents with a need for care and support relied on some degree of unpaid care from their family and friends. The effect MS has, not only on the person's life that has the condition, but also on those close to them is significant. Any effective treatment for MS would lead to more people remaining independent for longer and therefore delay the point when they may need to rely on support from carers. In turn this would lead to carers experiencing greater independence allowing them the space to focus on their own health and wellbeing. One carer told us "I have cared for my wife for over 30 years with MS. At first she had a slight limp, but over the years has gradually lost mobility. Now she constantly needs walking aids, and has not enough energy for more than about 20 feet. Last year she had a fall and was in hospital for 3 weeks. In April she had a second fall and is now in constant pain. Anything that can slow the disease progress further will help stabilise her decline, and greatly improve my own outlook, which currently looks bleak." Another explained "I now struggle to do most things that make life bearable. I fall a lot, can walk for only a few minutes and have lost all confidence and sense of self worth. My husband sees MS before he sees me and treats me as a patient and we mourn what we once were." References: 1. My MS My Needs survey 2019: UK findings -MS Society External template	is now recommended in the FAD.
6	Consultee	MS Society	**Relapse rate and disability progression** Ponesimod 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 teriflunomide. Ponesimod was found to be superior to teriflunomide on no evidence of disease activity (NEDA) status. Rates of confirmed disability accumulation 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. 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 the CRIMSON study (2) which aimed to improve understanding of how people with relapsing MS weigh up the pros and cons of different DMTs. It demonstrated the various and interrelated factors informing a person's choice of treatment. It was concluded that effects on long term disability progression may be seen by some people with MS as relating to future long term health	Thank you for your comment. Committee recommendations were made using the best available evidence.. Ponesimod is now recommended in the FAD.

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			outcomes, whilst relapse reduction can represent a more immediate or shorter-term impact on MS symptoms. Clearly, longer term outcome data is required to assess ponesimod's effects on disability progression relative to its comparator, 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. **References:** 1. 2014, The UK patient experience of relapse in Multiple Sclerosis treated with first disease modifying therapies - Multiple Sclerosis and Related Disorders (msard-journal.com) 2. The CRIMSON Study, 2018. Understanding treatment decisions from the perspective of people with relapsing remitting multiple Sclerosis: A critical interpretive synthesis - White Rose Research Online	
7	Consultee	MS Society	**The value of a treatment proven to reduce fatigue** Fatigue is one of the most commonly reported invisible symptoms by people with MS, with many finding it's the symptom that affects them most. Fatigue can have enormous, varied effects on daily life which may not be clearly reflected by a person's EDSS score. In clinical trial, ponesimod was significantly better than teriflunomide in scores of MS related fatigue, as reported by patients through the new Fatigue Symptoms and Impacts Questionnaire-Relapsing Multiple Sclerosis (FSIQ-RMS) outcome measure. Whilst we understand that ponesimod cannot be compared with any DMT other than teriflunomide on measures of fatigue as the FSIQ-RMS measure was not used in prior clinical trials, we would emphasise the scale of the unmet need for any treatment proven to reduce levels of MS related fatigue.	Thank you for your comment. The views of clinical experts and patient/carer representatives were considered by the Committee when formulating its recommendations. Ponesimod is now recommended in the FAD.
8	Consultee	MS Society	**Family planning** MS is the most common disabling neurological condition of young adults. Many who have MS are diagnosed in their twenties and thirties, at a time when people may be considering starting a family. The preliminary recommendations may therefore have a different effect on younger women and those considering pregnancy than on the wider population, with age and pregnancy both being protected characteristics. A 2020 study (1) reported that women with RRMS who are considering future pregnancy prefer to use DMTs with more favourable reproduction-related attributes, even when not trying to conceive. The study showed that reproductive issues also influenced people's preferences for DMT attributes that	Thank you for your comment. The views of clinical experts and patient/carer representatives were considered by the Committee when formulating its recommendations. Ponesimod is now recommended in the FAD.

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			were not directly related to pregnancy, with preferences dependent on the life circumstances in which choices were made. The short half-life of ponesimod may also impact on family planning for men. One person we spoke to emphasised family planning as a key factor for him in treatment choice, saying "as I yet do not have children and I want to become a father, information about the DMT's impact on fatherhood is important."	
9	Commentator	Novartis	Para 3.2: "…stating it did not consider ponesimod would not be used for secondary progressive multiple sclerosis." The construction of this statement regarding the potential use of ponesimod in SPMS is inaccurate; Novartis suggests this be reworded to "…stating it considered that ponesimod would not be used for secondary progressive multiple sclerosis."	Thank you for your comment. This section has been amended accordingly for clarity.
10	Commentator	Novartis	Para 3.2: "…agreed to define it" [*i.e.*, highly active disease] "as people whose disease progressed or remained unchanged within the last year despite having previous disease-modifying treatment" This statement regarding the definition of highly active disease is imprecise and potentially misleading in the context of the wording of DMT licences and the NHS treatment algorithm. Please clarify whether the analyses presented for this subgroup required "disability progression" (which is not usually part of the definition of highly active disease) or whether the phrasing "disease progression" was instead intended to cover the occurrence of relapses and/or MRI signs of inflammatory activity, as would be consistent with the subgroup definitions in the DMT licences/NHS algorithm; each of these three potential interpretations of the criteria (one of which is not ordinarily included in the definition) ought to be explicitly defined when describing the subgroup analysis. Please additionally clarify whether the analyses presented required the disease activity and/or progression to have occurred while patients were on treatment or whether the criterion of prior DMT was independent of the occurrence of activity and/or progression.	Thank you for your comment. This section has been amended to show the current definition of highly active disease used in NHS practice. Please note that there are multiple definitions of highly active disease and we are working to ensure consistency of definitions between decisions.
11	Commentator	Novartis	Para 3.9: "The committee considered that this anomalous result" [*i.e.*, cladribine having a higher treatment effect than other DMTs in the subgroup] "needs exploring further, particularly if there were any characteristics from the cladribine trials which could explain this." Novartis agrees with the clinical experts quoted in the ACD and with the Committee conclusion that this result is anomalous and not aligned to the findings of other NICE technology appraisals of DMTs for MS. Novartis would note the approach taken in TA699 where the NMA of the trial ITT populations for each DMT was accepted by the Committee as generalisable to each of the subgroups in the scope, as there is no evidence that subgroup membership is itself a treatment effect modifier. This approach generated effect estimates for cladribine that are in line with the clinical expert opinion quoted in the ACD and would be consistent with the conclusions of a recent prior appraisal.	Thank you, this comment has been noted.
12	Commentator	Novartis	Para 3.10: [re pooling interferons] "Further information on how well alternative approaches to pooling	Thank you for your comment.

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			fit the data, and further sensitivity analysis showing the effect of different network meta-analysis assumptions on the cost-effectiveness estimates would be needed." Novartis agrees with the Committee that the principle of pooling interferon data in the NMA (using appropriate statistical methodology) should be explored. However Novartis considers it important to separately analyse the cost-effectiveness of each interferon using the separate confidential net prices to the NHS in the cost-effectiveness analyses.	Evidence for both pooled and separate interferon data was provided, and both were considered by the Committee during its decision making.
13	Commentator	Novartis	Para 3.12: "The committee noted that many assumptions in the model had been accepted in previous technology appraisals in multiple sclerosis, including: … incorporating a treatment waning effect of 25% reduction in efficacy from years 2 to 5 and a 50% reduction in efficacy from year 6 onward …" Novartis disagrees with this statement and considers it to be a misleading description of the use of arbitrary waning assumptions in prior appraisals. The inclusion of waning assumptions has varied considerably across recent appraisals, with the Committee concluding that no arbitrary waning should be included in the economic model in both TA699 and TA533. Furthermore, in those appraisals where the Committee have included arbitrary waning, the values used have varied considerably. Notably in TA527 arbitrary waning was assumed to apply only from Year 11 onwards (with a straight drop to 50% efficacy). The specific waning assumptions reported in the ACD have therefore only been accepted by the Committee in 2 of the 5 positive NICE recommendations for DMTs in RRMS published since 2018 (TA616 and TA624), which is not the impression given by the ACD text. Novartis requests that the Committee note that Committee preferences as to the inclusion or not of an arbitrary waning assumption, as well as the timepoints and values of any arbitrary waning applied have varied significantly across appraisals.	Thank you for your comment. This has been amended in Section 3.12 of the FAD.
14	Commentator	Novartis	Para 3.12: "However, it acknowledged that a model that can simulate treatment sequencing and variable treatment waning would be complex to construct and difficult to populate because of limited data." Novartis welcomes the Committee's realism as to the data available for modelling, in reaching this conclusion. Novartis supports the acceptance of the well-established model structure for assessing RRMS DMTs.	Thank you, this comment has been noted.
15	Commentator	Novartis	Para 3.15: "The committee concluded that the model did not allow for treatment sequencing that would reflect clinical practice and that including only costs but not the treatment effect of siponimod was not fully consistent." Novartis welcomes the Committee's conclusion and reemphasises that including the costs of siponimod without including its beneficial effect is fundamentally biased and methodologically inappropriate.	Thank you, this comment has been noted.
16	Consultee	Multiple	The MS Trust is extremely disappointed that NICE is unable to recommend ponesimod as an NHS	Thankyou, this comment has

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		Sclerosis Trust	treatment for active relapsing remitting MS. We note that the committee recognises that ponesimod reduces the number of relapses compared with teriflunomide but finds that ponesimod'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. Having an additional first or second-line treatment would offer people with MS and clinicians greater scope for personalised treatments.	been noted. Ponesimod is now recommended in the FAD.
17	Consultee	Multiple Sclerosis Trust	**Ponesimod would be a valuable additional oral treatment** Ponesimod would be a valuable alternative to the two oral treatments currently used for active relapsing remitting MS: dimethyl fumarate and teriflunomide. Ponesimod 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. Ponesimod does not cause gastrointestinal problems and would be welcomed by clinicians and	Thank you for your comment. The views of clinical experts and patient/carer representatives were considered by the Committee when formulating its recommendations. Ponesimod is now recommended in the FAD.

[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.

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			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 was associated with a higher relapse rate and higher discontinuation rate due to disease breakthrough[5]. • **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.	
18	Consultee	Multiple Sclerosis Trust	**Earlier access to a more effective oral treatment** There are currently no oral drugs routinely available as first-line treatments for people who have only had one relapse in the last two years. Both dimethyl fumarate and teriflunomide require people to have 2 significant relapses in last two years, which carries the risk of accumulating additional disability from additional relapses and “silent” MS activity resulting in further lesions. People with MS are increasingly aware of the significance of reducing or eliminating signs of sub-clinical disease activity in improving long term outcomes. There is a growing recognition that regular clinical evaluation and regular MRI scans are required to fully assess MS activity and response to disease modifying drugs.	Thank you for your comment. The views of clinical experts and patient/carer representatives were considered by the Committee when formulating its recommendations. Ponesimod is now recommended in the FAD.

[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

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			The majority of people with relapsing remitting MS are eager to start treatment with one of the disease modifying drugs and aware of the importance of starting treatment as soon as possible after diagnosis. Waiting for a second relapse to happen in order to start a treatment is a major source of anxiety. Access to ponesimod would allow people with MS to start treatment earlier and with a more effective treatment than beta interferons and glatiramer acetate. There is strong clinical evidence that early and more effective treatment results in better long term disability outcomes.	
19	Consultee	Multiple Sclerosis Trust	**Ponesimod's effect on progression of disability is unclear** **We urge the committee to reconsider their conclusions on disability progression in the context of previous NICE appraisals for disease modifying treatments.** In clinical trials, ponesimod showed a numerical improvement in confirmed disability progression compared to teriflunomide, although this was not statistically significant. The Committee has previously concluded that teriflunomide may have a beneficial impact on accumulation of disability (TA303). This leads to the conclusion that ponesimod significantly reduces disability progression compared to best supportive care and is at least as effective as teriflunomide, if not more effective. A recent study found that it can take up to 16 months for a disease modifying drug to have a full clinical effect on disability progression[7]. In the case of fingolimod, the therapeutic lag was 11 months. This would suggest that a two-year clinical trial is not long enough to see a significant difference between active comparators, particularly for six month confirmed disability progression. A review of NICE FADs (see below) shows that in previous appraisals, the Committee has recognised that the majority of disease modifying treatments significantly reduce disability progression when compared to best supportive care but not when compared to active comparator. **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–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.	Thank you for your comment. The committee considered all evidence submitted. The views of clinical experts and patient/carer representatives were considered by the Committee when formulating its recommendations. Ponesimod is now recommended in the FAD.

[7] Roos I, et al. Delay from treatment start to full effect of immunotherapies for multiple sclerosis. Brain 2020; 143(9): 2742-2756.

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			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.	
20	Consultee	Multiple Sclerosis Trust	**Mechanism of action** Ponesimod 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.	Thank you for your comment. The Committee considered all the evidence submitted, including evidence from clinical trials, patient and clinical experts, the Assessment

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			Ponesimod 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, ponesimod might be expected to cause fewer side effects compared to fingolimod. Approval of ponesimod would allow clinicians and patients to access this proven, very effective mechanism of action as a first line treatment.	Group's economic analysis and the companies' submissions. Ponesimod is now recommended in the FAD.
21	Consultee	Multiple Sclerosis Trust	**Conclusion** Ponesimod would be a valuable additional treatment for active relapsing remitting MS. Once daily oral route of administration means that ponesimod can be taken at home, eliminating potential delays in starting treatment which have occurred with other disease modifying drugs which require access to outpatient infusion clinics. Overall, this route of administration minimises demands on NHS services. Fatigue is one of the most common and debilitating symptoms of MS and can be one of the most challenging to manage and treat. Ponesimod's potential for improvement, or at least stabilisation, of fatigue levels will be a significant advantage for people with MS. Ponesimod is rapidly eliminated and lymphocyte counts return to normal range within 1 week. This will be beneficial for people needing vaccination, in cases of serious infection or for women who want to start a family. The impact of certain disease modifying drugs (particularly ocrelizumab, ofatumumab, fingolimod, alemtuzumab) on the effectiveness of Covid vaccination has been an increasing cause of concern for patients and clinicians. Titration of the first dose of ponesimod minimised first-dose cardiac effects; people with MS will not need to be monitored in a hospital clinic while taking the first dose, as is required for fingolimod. 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.	Thank you for your comment. The committee considered all evidence submitted. The views of clinical experts and patient/carer representatives were considered by the Committee when formulating its recommendations. Ponesimod is now recommended in the FAD.
22	Consultee	Janssen-Cilag	**Comment 1.1. The pooled interferon class-based model had good fit and is appropriate for decision making. (ACD 3.10 – page 11)** As requested by the Committee, the model fit statistics for the pooled interferon class-based NMAs are provided in table 1. It was not possible to incorporate the results of trials which compared interferon vs interferon in these analyses i.e., where the only eligible interventions were interferon regimens, given that such trials	Thank you for providing this additional analysis as requested by the Committee. It was helpful in aiding their decision making.

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			did not provide comparative data between interferon and another regimen of interest, and thus could not be included in a network in which all interferons were pooled in a single node. This resulted in 4 trials being excluded: EVIDENCE (Panitch, et al., 2002), INCOMIN (Durelli, et al., 2002), Mokhber, et al., 2015., and REFORMS (Singer, et al., 2012) trials. Random vs. fixed effects models were selected based on best fit i.e., a lower deviance information criterion (DIC) value, and inconsistency analyses were performed considering only the model with better fit. For annualised relapse rate (ARR), and 3-month and 6-month confirmed disability accumulation (CDA) the fixed effect model produced the best fit, whereas for treatment discontinuations the random effects model produced the better fit. Overall, consistent/inconsistent model for ARR (fixed effect models (FE)) and treatment discontinuations (random effect (RE) vague models) had similar model fit. **Table 1 Model fit statistics for pooled interferon class-based NMAs (consistent and inconsistent model)**	

Diagnostic	Consistent model		Inconsistent model	
	Random effects with vague priors	Fixed effects	Random effects with vague priors	Fixed effects
ARR				
Deviance information criterion (DIC)				
Total residual deviance				
SD				
3-month CDA				
Deviance				

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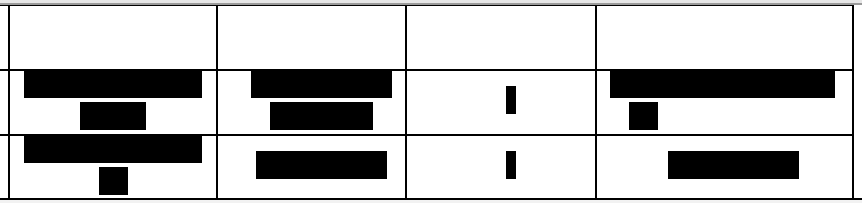
			information criterion (DIC)  Total residual deviance SD *6-month CDA* Deviance information criterion (DIC) Total residual deviance SD *Treatment discontinuations* Deviance information criterion (DIC) Total residual deviance SD Note: the model with better fit was determined based on a lower deviance information criterion (**bolded)**. *Analysis of inconsistency was not conducted. Inconsistency analyses were conducted for the base case analysis only (fixed effects for ARR and CDA outcomes; random effects for the treatment discontinuations outcome).	
23	Consultee	Janssen-Cilag	**Comment 1.2 Analysis of inconsistency in the pooled interferon class-based analyses: overall, ARR, 3-month and 6-month CDA and treatment discontinuations demonstrated good consistency (ACD 3.10 – page 11)** In addition to the request for model fit statistics, the Committee noted that it would also be useful to see an inconsistency assessment for the NMA of pooled interferons. An important assumption underlying the NMA is that the analysed network is consistent, meaning that there is no evidence of disagreement between	Thank you for providing this additional analysis as requested by the Committee.

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			the direct and indirect evidence being combined. (Dias, et al., 2011) For example, whether the direct evidence of ponesimod vs placebo through the phase 2 ponesimod trial is in alignment with indirect evidence e.g., via OPTIMUM (ponesimod v teriflunomide) and then TEMSO (O'Connor, et al., 2011)/TOWER (Confavreux, et al., 2014) (teriflunomide v placebo). An unrelated mean effects model (i.e., an inconsistency model) based on the NICE technical support document (TSD) 4 was used to assess potential inconsistency. (Dias, et al., 2011) To identify any loops where inconsistency was present, the posterior mean deviance of: i) individual data points for ARR and all-cause treatment discontinuations, and ii) individual studies for 3-month and 6-month CDA, in the inconsistency models was plotted against the posterior mean deviance in the consistency models. Below we present the results for the posterior mean deviance for ARR, 3-month CDA, 6-month CDA and treatment discontinuations. On the plots, consistency is assessed by considering how close all points are to the line X=Y (consistent NMA = inconsistent NMA). The inconsistency results for ARR, 3-month CDA, 6-month CDA and treatment discontinuations signify that the outcomes generally demonstrated good consistency. For 3-month and 6-month CDA, the DIC was significantly lower in the inconsistent model (a difference of 5 or more is considered significant, based on NICE TSD 3 (Dias, et al., 2011)). However, the deviance information criterion and total residual deviance and the posterior deviance (Figures 1-4) were similar between the consistent/inconsistent model (FE model). Therefore, it can be concluded that the consistency assumption was not violated. Outliers are any points where posterior deviance (for either the consistent or inconsistent model) is substantially high. Alternatively, a potential inconsistency is signalled in cases where the posterior deviance is very different between the	

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			inconsistent and consistent models (points fall outside of the line X=Y). Some outliers exist, but these are not unexpected given the heterogeneity that we know is present in multiple sclerosis (MS) trials owing to the age of some trials, the difference in outcome definitions and the results from some trials not always aligning with expert clinical knowledge of the products. Outlier effects in these plots may also arise due to random chance in these analyses. The red points in the figures below highlight potential inconsistencies and outliers in the results i.e., these are not necessarily inconsistencies in the results, but may be potential sources. Similarly, outlier points do not necessarily indicate an inconsistency, but they point to potential outliers. Furthermore, some of the outlier studies had similar results for consistent and inconsistent analyses i.e., they fell on the line – this indicates there was no impact on fit. Overall, we note that the pooled NMA results are generally representative of the results that would be expected in clinical practice, this was also noted by the clinical experts at appraisal committee meeting (ACM) 1, who commented that "*the results of the network meta-analyses generally reflected which treatments are considered more effective in the NHS*". Please note for figures 1- 4 the X and Y axis are not on a comparable scale. **Figure 1 Posterior Mean Deviance for ARR, Consistent versus Inconsistent model (Fixed Effects)**	

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			 For the ARR outcome, overall, the results satisfy the consistency assumption and there was generally no disagreement between the models. However, the CombiRx (Lubin, et al., 2013) trial was an outlier: it should be noted that the reported ARR for both arms of the trial were lower than the ARR reported for the same treatments in other trials. Authors of the primary publication for CombiRx (Lubin, et al., 2013) acknowledged this finding: "*The protocol defined ARRs are among the lowest reported to date for the agents utilized in this study, or any other pivotal study with other MS therapeutic agents that utilized similar definitions.*" Authors suggested that a more rigid definition of relapses in CombiRx (Lubin, et al., 2013) was a potential reason for these findings. Additionally, in the analyses of ARR, the alemtuzumab 12mg (once daily) arm of CAMMS223 (Panitch, et al., 2008) was highlighted due to high posterior deviance. But in this particular case, falling on the line indicates there is not a consistency issue. Therefore, this is not a violation of the consistent assumption of the NMA as the deviance was high in both models. Moreover, the treatment effect estimates were similar between the consistent and inconsistent model, suggesting no disagreements between the two models (thus, not a concern from a consistency standpoint). Therefore, as an	

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			overall conclusion ARR results from the pooled interferon class-based model are appropriate. **Figure 2 Posterior Mean Deviance for 3-month CDA, Consistent versus Inconsistent model (Fixed Effects)**  For the analysis of 3-month CDA, there were no trials that were highlighted as potential inconsistencies in the data despite there being some trials appearing far from the line it is important to note that the Y axis is numerically not as high as the Y-axis for ARR. Overall, it can be concluded that the consistency assumption was not violated as the posterior deviance from the consistent/inconsistent models were relatively similar i.e., the points fell close to the line Y = X **Figure 3 Posterior Mean Deviance for 6-month CDA, Consistent versus Inconsistent model (Fixed Effects)**	

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			 Similar to the analysis of ARR, for the 6-month CDA (Figure 3), CAMMS223 (Panitch, et al., 2008) was also highlighted because it had high posterior deviance (it should be approximately 1 but it was about 3.6 in both models). This suggests that both models did not fit the study well. However, this is not a violation of the consistent assumption of the NMA as the deviance was high in both models. The treatment effect estimates were similar between the consistent and inconsistent model, also suggesting no disagreements between the two models (thus, not a concern from a consistency standpoint). Therefore overall, it can be concluded that the consistency assumption was not violated as the posterior deviance from the consistent/inconsistent models were relatively similar i.e., the points fell close to the line Y = X. **Figure 4 Posterior Mean Deviance for Treatment discontinuations, Consistent versus Inconsistent model (Random Effects with Vague Priors)**	

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			 In the analysis of treatment discontinuation, the phase 2 study of ocrelizumab was highlighted as a potential source of inconsistency. Again, it is noted that the treatment effect estimates were similar between the consistent and inconsistent model suggesting no disagreements between the two models (thus, not a concern from a consistency perspective	
24	Consultee	Janssen-Cilag	**Comment 1.3. The hierarchical class-based model may be an appropriate analysis for decision making, but the ADVANCE and INCOMIN trials are outliers and should be excluded based on their clinically implausible results as clinical expert feedback from the ofatumumab and ocrelizumab appraisals. (ACD 3.10 – page 11)** To fulfil the Committee's, request a class effect hierarchical NMA model based on Dias, et al., 2018 was applied to data of the main analysis submitted previously. The class effect hierarchical NMA model is an extension of the standard NMA models from NICE TSD 2 (Dias, et al., 2011) where therapies with similar mechanisms of action fall into the same class and their treatment effects are	Thank you for your comment. It was noted by the Committee during decision making.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			modelled as exchangeable. The hierarchical model assumes the relative effects of treatments within a class come from a common class distribution (i.e., the relative effects are exchangeable). Exchangeability is a key assumption of hierarchical models and assumes that all treatment effects within a class are similar. This assumption allows the model to borrow data (or strength) from treatments within the same class. Furthermore, it is possible to include studies that compare treatments within the same class in the class effect hierarchical NMA model. These studies are useful for informing the within-class variability. It should be noted that this method uses random effects to model class effects which introduces additional variability in the treatment effect resulting in wider credible intervals. However, we have accounted for the credible intervals in the iterations run in the probabilistic model results i.e., we ran 10,000 iterations of the results (see comment 4.2 - 4.3). The hierarchical class-based model can include all interferon trials reporting eligible outcome data, including trials which compared interferons to interferons, which was not possible in the pooled interferon NMA analysis submitted previously. However, since all studies of interferons contribute to the interferon class estimates, it was considered important to carefully consider potential violations of the exchangeability assumption for these analyses, and as such it was decided that the ADVANCE and INCOMIN trials be excluded. The exclusion of both ADVANCE and INCOMIN are consistent with the most recent appraisal of ofatumumab (TA699) and were also discussed in the appraisal of ocrelizumab (TA533). There are also sources of data, including publications and clinical expert opinion, that note the unexpectedly high efficacy in the two trials and therefore deems them to be outliers. We discuss some of the issues with these trials below: • <u>ADVANCE trial (peginterferon)</u> The ADVANCE trial was a phase 3, double-blind, multi-centre, placebo controlled randomised controlled trial, which lasted 48 weeks. After the initial 48-week period	

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			of the trial, patients in the placebo group were re-randomised in a 1:1:1 ratio to receive either an injection of peginterferon beta-1a 125 mcg every 2 weeks or every 4 weeks, or alternatively to receive placebo, for a double-blind controlled period of 48 weeks. It is important to note that only the 2-week dosage frequency is licensed and used in clinical practice. (NICE, 2020) In recent appraisals the ADVANCE trial was excluded from the NMAs of ofatumumab (TA699) (NICE, 2021) and ocrelizumab (TA533) (NICE, 2018) with ERG and Committee agreement, because peginterferon was shown to be more effective than other beta-interferons and high-efficacy treatments such as natalizumab, (which is contrary to clinical experience and is clinically implausible). In the appraisal of ocrelizumab (TA533) (NICE, 2018) the NICE Committee found clinically implausible results were caused by inclusion of the ADVANCE trial in an NMA of time to 6-month confirmed disability progression (CDP-6). In the appraisal of ofatumumab (TA699) (NICE, 2021), the Committee agreed the trial was an outlier. It was originally discussed by the clinical experts in the appraisal of ocrelizumab (TA533) (NICE, 2018) (and revisited during the appraisal for ofatumumab [TA699]) that the fact that results from ADVANCE showed peginterferon as having greater efficacy as natalizumab lacks clinical face validity. In addition, in the multiple technology appraisal (MTA) of beta interferons and glatiramer acetate (TA527) (NICE, 2018) the Assessment Group report noted "(peginterferon), *in particular, relied on one trial with one year of follow-up connected to evidence networks only via placebo.*" Given that class estimates for interferon would be particularly impacted by violations of the assumption of exchangeability, it was deemed unsuitable to include such a flawed trial, which has been cautiously examined in several previous appraisals to be inappropriate, and as such the class estimates could be greatly impacted by an outlier trial. (NICE, 2021).	

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			• INCOMIN (interferon beta 1b) The INCOMIN trial was a 2-year, prospective, randomised, multicentre trial, comparing interferon beta-1b every other day to interferon beta-1a weekly. The INCOMIN trial was randomised, but it was an open-label trial. INCOMIN only included 188 participants. Discussed originally in the appraisal of ocrelizumab (TA533) and also in the appraisal of ofatumumab (TA699), the results of INCOMIN were noted to be inconsistent with results from phase 3 trials of interferon 1b and 1a in that, INCOMIN found patients receiving interferon beta-1b every other day had improved outcomes compared to patients receiving a weekly dose of interferon beta-1a. During the appraisal of ofatumumab (NICE, 2021), the company noted that INCOMIN was an "*outlier and not reflective of clinical practice*" in which the ERG agreed. Additionally, several other studies indicated no clinically significant differences between the two treatments (Vartanian, 2003), which is generally in line with clinical opinion. In both the appraisal of ocrelizumab (TA533) and ofatumumab (TA699), the Committee agreed that the results produced by the INCOMIN study were clinically implausible, and therefore that it was an outlier trial. Again, for the reasons stated above, it was considered inappropriate to include the INCOMIN study in the hierarchical NMA. We would also like to note that it is not possible to include results for INCOMIN in either the 3-month or 6-month disability network due to 3-month disability not being reported and 6-month not being reported in the form of a hazard ratio. Therefore, it would only be possible to report INCOMIN for ARR and treatment discontinuation. (NICE, 2021).	
25	Consultee	Janssen-Cilag	**Comment 1.4 Overall, the results of the hierarchical class-based interferon NMA are broadly aligned to the pooled interferon class-based NMA**	Thank you for providing this additional analyses as requested by the Committee; it was considered during decision making. They agreed that while

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			The requested class-based hierarchical model uses random effects to model the class-based effects. The class effect hierarchical model is used when there are treatments in the network with similar mechanisms of action, and where it is reasonable to assume that there is alignment in the action of treatments from the same class. This contrasts with the standard NMA model from NICE TSD2 (Dias, et al., 2011) where treatments in a network are assumed to be independent of each other. Overall, the fit of this model is similar to the previous NMAs based on total residual deviance. Due to the hierarchical model utilising random effects to model class effects, the wider credible intervals observed with the hierarchical model are expected, however we do note that between-trial heterogeneity is an issue across the network. This could be a rationale for not using the more complex hierarchical approach and instead using results from the original pooled interferon class-based NMA, and at the least for considering the pooled interferon NMA as potentially more appropriate. • <u>Annualised Relapse Rate (ARR)</u> In general, the median estimates of the class-level treatment effects from the hierarchical class-based model are aligned with previously conducted analyses where interferon regimens were pooled. The effect estimates from the hierarchical class-based model have wider credible intervals. Despite the wide credible intervals, the results for ARR are broadly consistent with the results seen in the previous pooled interferon class based NMAs, with the most effective treatments being the monoclonal antibody treatment ofatumumab, natalizumab, ocrelizumab and alemtuzumab.	the point estimates align, the wide credible intervals reflect the overall uncertainty of the analyses and may have been modelled incorrectly. Further information about their conclusions can be seen in section 3.10 of the FAD.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			Figure 5 Forest Plot (Ponesimod versus Treatments) for ARR (excluding ADVANCE and INCOMIN): Interferon Class Treatment Effect; Fixed Effects Model for Individual Effects  • 3-month CDA In general, the median estimates of the class-level treatment effects from the hierarchical class-based model are aligned with previously conducted analyses where interferon regimens were pooled. Again, the effect estimates from the hierarchical class-based model have wider credible intervals. For 3-month CDA, again we note the trend that ofatumumab, ocrelizumab and alemtuzumab are indicated as being more effective than ponesimod, with the remaining treatments being similar or less effective than ponesimod. **Figure 6 Forest Plot (Ponesimod versus Treatments) for 3-month CDA [excluding ADVANCE]: Interferon Class Treatment Effect; Fixed Effects Model**	

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			 • 6-month CDA Overall, the 6-month CDA median estimates from the hierarchical class-based model are aligned with previously conducted analyses where interferon regimens were pooled and again demonstrate wider confidence intervals. For 6-month CDA, ofatumumab, ocrelizumab, alemtuzumab and natalizumab are indicated as being more effective than ponesimod, with the remaining treatments being equal or less effective than ponesimod. **Figure 7 Forest Plot (Ponesimod versus Treatments) for 6-month CDA [excluding ADVANCE trial]: Interferon Class Treatment Effect; Fixed Effects Model**	

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			 • Treatment discontinuations Similar to efficacy outcomes, the median estimates of the class-level treatment effects for treatment discontinuations are aligned with previously conducted analyses where interferon regimens were pooled. The effect estimates also have wider credible intervals, but again this is due to the nature of the model and is to be expected. **Figure 8 Forest Plot (Ponesimod versus Treatments) for Treatment Discontinuations [excluding ADVANCE & INCOMIN trials]: Interferon Class Treatment Effect; Random Effects with Vague Priors**	

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			 **Comment 1.5 Model fit statistics for hierarchical class-based model: the hierarchical class-based NMA model generally fit the data well** For transparency, we have provided the Committee with model fit statistics for the hierarchical class-based NMA. Generally, no clear gains/losses were found in terms of model fit (based on total residual deviance). The hierarchical class-based model fit the data relatively well, based on the total residual deviance being close to the number of data points, for each outcome. Overall, there were uncertainties with the class effect as the 95% credible intervals of the standard deviations (SDs) was wide for all outcomes, but with this type of model this is to be expected. Overall, the hierarchical class-based NMA model is appropriate for decision making, furthermore the overall conclusions based on the point estimates of the hierarchical NMA are broadly in line with the conclusions of the previously conducted pooled interferon class NMA.	

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<tr><th>Comment number</th><th>Type of stakeholder</th><th>Organisation name</th><th>Stakeholder comment
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Please respond to each comment</th></tr>
<tr><td></td><td></td><td></td><td>Table 2 Model fit statistics for hierarchical class-based model analyses

<table><tr><th>Diagnostic</th><th>ARR (fixed effects)</th><th>3-month CDA (fixed effects)</th><th>6-month CDA (fixed effects)</th><th>Treatment discontinuations (random effects with vague priors)</th></tr><tr><td>Deviance information criterion (DIC)</td><td></td><td></td><td></td><td></td></tr><tr><td>Total residual deviance</td><td></td><td></td><td></td><td></td></tr><tr><td>Beta</td><td></td><td></td><td></td><td></td></tr><tr><td>SD for individual level effects</td><td></td><td></td><td></td><td></td></tr><tr><td>SD for class level effects</td><td></td><td></td><td></td><td></td></tr></table></td><td></td></tr>
<tr><td>26</td><td>Consultee</td><td>Janssen-Cilag</td><td>Comment 2.1. Analysis using updated mortality assumptions informed from new evidence: the updated mortality data from Harding et al 2018 improves QALY outputs for patients and aligns economic model outputs closer to outputs the Committee would expect (ACD 3.10 – page 11)

In line with this request, we have reviewed the Harding, et al., 2018 paper and subsequently input the mortality states into the economic model. For completeness we were required to make some assumptions: the Harding, et al., 2018 paper only reported mortality ratios for EDSS 4 - 9 and they grouped EDSS 4 and EDSS 5 together. Therefore, we have selected the following rules to complete the EDSS states in the most methodologically appropriate way:
• EDSS 0 - 3 uses the current base case value derived from the Pokorski 1997
• EDSS 4 - 5 use the same value from Harding 2018
• EDSS 6 - 9 use individual values from Harding 2018.</td><td>Thank you for providing this additional analysis as requested by the Committee; it was considered during decision making. Further information about their conclusions can be seen in section 3.14 of the FAD.</td></tr>
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<tr><th>Comment number</th><th>Type of stakeholder</th><th>Organisation name</th><th>Stakeholder comment
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Please respond to each comment</th></tr>
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The main difference between Pokorski, 1997 and Harding, et al., 2018 is on the higher EDSS mortality risk i.e., EDSS 8 and 9, this is where the Committee were most interested in observing changes in the updated mortality data and where the greatest change can be seen in the scores. Due to missing EDSS states and the lower impact of disease in 0-3, it is more appropriate to utilise the Pokorski, 1997 data to complete the EDSS scale. A source of data was required to fill the gap in the missing data from Harding, et al., 2018. Therefore, given that mortality is not a key driver in EDSS 0 - 3 we utilised the Pokorski data to fill the gap, but don't anticipate much impact from this, and believe that the Pokorski data is the most appropriate source.

To test the impact of changes that the mortality data update had on the model, we captured the quality adjusted life year (QALY) outputs using the pooled NMA model and with the Pokorski et al 1997 data and then also with the new Harding, et al., 2018 data. The results are detailed in table 3 below.

Table 3 Mortality outputs based on a comparison of Pokorski vs Harding et al

<table>
<tr><th></th><th>Pone-simod</th><th>Terifluno mide</th><th>DMF</th><th>GA</th><th>IFN Class</th><th>Ocreli-zumab</th><th>Ofatu-mumab</th></tr>
<tr><td>Pokorski et al 1997 data</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>QALYs</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Patients</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Caregivers</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Harding et al 2018 data</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>QALYs</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Patients</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Caregivers</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
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Overall, there was an increase in QALYs with the new mortality data, by approximately 1 QALY, although there was slightly more of a QALY increase for
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Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			glatiramer acetate and ofatumumab than for the other comparator treatments. The new mortality data did not significantly change the estimates of cost-effectiveness. But as expected, total life years decreased (by ~4 years) with the new mortality data. The total QALYs increased, however, due to more patients dying from the high EDSS states (NB – patients in EDSS 8 and 9 have negative utility values so they are worse off than the dead patients for the purpose of the economic model).	
27	Consultee	Janssen-Cilag	**Comment 3.1 Overall the ponesimod model's QALYs are consistent with those in recent appraisals of ofatumumab (TA699) and peginterferon (TA624). The outputs for beta interferons and glatiramer acetate (TA527) are unusually high, but it is not possible to determine why this is, due to a lack of details around the inputs used in TA527.** To understand further if the modelled outputs for ponesimod were aligned to previous appraisals it was possible to review recent NICE comparator MS appraisals input data. However, it is important to note that several of the outputs from published appraisals are heavily redacted, so we believe the most appropriate method of exploration and alignment is via an assessment of the available QALYs from unredacted appraisals. We reviewed the more recent NICE appraisals in MS, (since older appraisals may not align on outputs appropriately) including the appraisals of ofatumumab (TA699) (NICE, 2021), peginterferon (TA624) (NICE, 2020) and the multiple technology appraisal (MTA) of beta interferons and glatiramer acetate (TA527) (NICE, 2018). Unfortunately, it was not possible to review the QALY outputs from ozanimod (TA706) (NICE, 2021) and ocrelizumab (TA533) (NICE, 2018), since all QALY information was redacted. Reviewing the three past appraisals provides a general understanding of the total QALYs gained from each treatment in its respective economic model. The outputs	Thank you for your comment.; it was considered during decision making. Their conclusions relating to this comment can be seen in section 3.13 of the FAD.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			in ofatumumab (TA699) (NICE, 2021) and peginterferon (TA624) (NICE, 2020) ranged from approximately 3.5 QALYs up to approximately 6 QALYs for higher efficacy treatments, and for treatments given to patients with highly active disease. It is important to note that there were variations in QALY outputs based on different input sources, the treatment population, and scenario analyses. However, generally the QALYs fell within the 3.5 to 6 range, except for the QALY outputs for the MTA appraisal of beta interferons and glatiramer acetate (TA527) (NICE, 2018). On average, the MTA QALYs were much higher than the other appraisals with QALY ranging from ~ 8 to ~10 QALYs, again depending on scenario and inputs. For a more direct comparison against the ponesimod model, we reviewed the three appraisals in further detail; ofatumumab (TA699) (NICE, 2021), peginterferon (TA624) (NICE, 2020) and the MTA (TA527) (NICE, 2018) with the aim of aligning model inputs to the ponesimod model to understand if the modelled outputs of ponesimod directly produced similar QALYs to those stated in the comparator's original submissions. To undertake this scenario analysis, we attempted to select the appraisal/s where most inputs were visible so that we could replicate these in the ponesimod model: • Comparison vs. TA699 (ofatumumab): we were able to align on some inputs, but not all required inputs due to a lack of detail provided and some redactions in the company submission, for example details of the NMAs. The difference in QALYs for common comparators for the ofatumumab base-case and ponesimod base-case presented at ACM 1 indicate that the QALY outputs are generally comparable to between the two models. However, it was not possible to take the analysis further to fully align on the model inputs, and we therefore could not use ofatumumab for the benchmarking exercise. • Comparison vs. TA527 (NICE MTA): Some of the key assumptions in the MTA model are excluding carer disutility and no MS-related excess	

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			mortalities. After aligning on those inputs, there is still a significant difference in the QALY output (5.1 ponesimod base-case vs. 9.6 in the MTA base-case from the Assessment Groups pooled base-case). It is possible the two models in the MTA used different natural disease progression transition probabilities (from RRMS to SMPS), but no details were provided. It was also very difficult to understand which were the key base-case assumptions for the model and what values were used. Due to this it was not possible to fully align on model inputs. The large QALY values from this appraisal are not consistent with the ponesimod model or the more recent appraisals in MS. Unfortunately, without access to the model and full model inputs it was not possible to explore why this is. • Comparison vs. TA624 (Peginterferon): the peginterferon model structure is very similar to the ponesimod model, additionally we were able to align on almost all the model inputs as these were detailed in the submission clearly, except for the treatment effects which were based on the company NMAs, which are redacted, and the life tables (very minimal impact). Despite this, there is enough available information to undertake scenario analysis with this appraisal. We explored scenarios using our original inputs based on hazard ratios as transition probabilities i.e., before they were converted to risk ratios by the ERG/Committee since this was in the pooled interferon ponesimod model and has been used in previous appraisals. To conduct the testing, we took the known inputs from the peginterferon appraisal and used them in the ponesimod model to try to replicate results detailed in the original peginterferon submission. Table 4 outlines each of the inputs used in the peginterferon model and where the original model does or does not align with the inputs in the ponesimod model. From the table there are 4 inputs that did not align between the two models, these are baseline characteristics, which come	

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from each company's respective trials, transition from RRMS to SPMS, treatment discontinuations and carer disutility. It is not possible to fully align to NMA outputs as these are confidential and are therefore redacted.

Table 4 Ponesimod model comparison to peginterferon (TA624)

<table>
<tr><th>Input</th><th>Peginterferon model source</th><th>Alignment with ponesimod model</th></tr>
<tr><td>Baseline characteristics</td><td>ADVANCE trial</td><td>Re-aligned to TA624*</td></tr>
<tr><td>Natural history RRMS</td><td>British Columbia</td><td>Original ponesimod model aligned with TA624</td></tr>
<tr><td>Transition from RRMS to SPMS</td><td>London Ontario</td><td>Re-aligned to TA624*</td></tr>
<tr><td>Natural history SPMS</td><td>London Ontario</td><td>Original ponesimod model aligned with TA624</td></tr>
<tr><td>Natural history relapse</td><td>UK MS survey/Patzold 1982</td><td>Original ponesimod model aligned with TA624</td></tr>
<tr><td>Treatment effect</td><td>6-month disability/relapse</td><td>Original ponesimod model aligned with TA624</td></tr>
<tr><td>Treatment discontinuation</td><td>All-cause from trial</td><td>Re-aligned to TA624*</td></tr>
<tr><td>Stopping rule</td><td>EDSS>=7/progression to SPMS</td><td>Original ponesimod model aligned with TA624</td></tr>
<tr><td>Waning</td><td>25% after 2 years/50% after 5 years</td><td>Original ponesimod model aligned with TA624</td></tr>
<tr><td>Utility</td><td>Orme et al 2007</td><td>Original ponesimod model aligned with TA624</td></tr>
<tr><td>Carer disutility</td><td>Acaster 2013</td><td>Acaster 2013 directly re-aligned to TA624*</td></tr>
<tr><td>Mortality</td><td>General population mortality (2016) and Pokorski et al 1997 (no interpolation)</td><td>General population mortality (2020) and Pokorski et al 1997 (interpolation)*</td></tr>
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Other notable inputs	NMA for disability and relapses redacted	NMA for disability and relapses from Janssen NMA*

*Deviates from Janssen base case analysis

The results of the scenario analysis comparison are detailed in table 5. The scenario analysis for the two sets of inputs, results in QALYs for comparators common to both appraisals ranging from [redacted] and [redacted]. This indicates that the QALY outputs are very comparable between the two sets of results for the ponesimod and peginterferon models. Overall, the QALY outputs from the pooled interferon ponesimod model were between just below 3 QALYs to just below 5 QALYs on average. This generally aligns to the outputs of the ofatumumab and peginterferon appraisal outputs of 3 QALYs up to ~6 QALYs and the number of QALYs was very comparable.

Table 5 Results of alignment between ponesimod and peginterferon (TA624)

Treatment	QALYs (Janssen model)	QALYs (peginterferon model inputs)	Difference
Teriflunomide	[redacted]	[redacted]	[redacted]
DMF	[redacted]	[redacted]	[redacted]
GA 20	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]

We note that while it was possible to isolate some of the key model inputs, it was not possible to assess the impact of the comparator company's NMA results, which we believe are likely to be a key driver in the small difference between the QALY outputs, alongside baseline characteristics. It is worth also noting that the company NMA results will have likely changed over time as more treatments become available. However, from the scenario analysis

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			the inputs which resulted in the most notable changes in QALY values include: - the Committee/ERG conversion of hazard ratios to risk ratios; this change did not have a significant impact on the QALY values but did reduce them on average by 1% - 3% depending on the comparator. This was not included in this scenario, but when reviewing the old model (pre-ACM 1 to post ACM 1) a small change in the QALYs was noted. - Removal of caregiver disutility, as was done in TA527 (potentially one contribution to the higher QALY values in the MTA) - Baseline characteristics – based on trial data. In conclusion, the outputs for the ponesimod model are comparable to the outputs from the most recent appraisals of peginterferon (TA624) (NICE, 2020) and ofatumumab (TA699) (NICE, 2021). There are differences in inputs based on trial data and the resulting NMA inputs, which are likely to have a significant impact on the results. Despite this, the overall range of QALYs between ponesimod and the two appraisals are broadly aligned. We also note that the QALY outputs from the MTA of beta interferons and glatiramer acetate (TA527) (NICE, 2018) are unusually high, but we cannot isolate the inputs due to a lack of clarity in the appraisal. Overall, we believe that the economic model based on the pooled interferon NMA is robust, consistent with previous appraisals and appropriate for decision making based on this comparison exercise with the most recent appraisals.	
28	Consultee	Janssen-Cilag	**Comment 3.2 Modelled outputs for time spent in SPMS from the ponesimod model are consistent with previous appraisals, notably peginterferon (TA624)** To explore the Committee's request to investigate the time spent in the SPMS state by patients in the ponesimod model, we have reviewed previous appraisals to understand which state patients spend most time in from other appraisals, and where possible we have conducted scenario analysis around the assumptions.	Thank you for providing this additional analysis as requested by the Committee; it was considered during decision making. Further information about their conclusions can be seen in section 3.13 of the FAD.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			After further exploration of the economic model and outputs (as discussed in comment 2.1) we observed that the ponesimod model's QALY estimates are related to the time spent in RRMS and SPMS states, since patients with SPMS (a) have lower utility and (b) are also more likely to progress to later disease stages, therefore they have lower utility values. To further understand the SPMS outputs the ponesimod model is producing, we conducted two activities: • a review of time spent in SPMS reported from the peginterferon appraisal for established comparators (due to the availability of unredacted inputs) • a scenario analysis putting peginterferon inputs into the ponesimod model to test outputs. We calculated the time spent in SPMS in the peginterferon model using the undiscounted life years reported in the TA624 appendix, Table 102. For example, the time spent in SPMS for teriflunomide is 65.5%, calculated as (34.46 total life years - 11.89 years spent SPMS free) / (34.46 total life years). Results from the Janssen model with ponesimod inputs compared to results produced replacing ponesimod model inputs with those from peginterferon are presented in table 6. For comparison, the table also includes the results of time spent in SPMS reported directly from the peginterferon appraisal. When comparing the time spent in SPMS directly from the peginterferon appraisal, it was observed that on average 65% of the time was spent in the SPMS disease state based on the peginterferon model, with patients spending the most time in SPMS when receiving glatiramer acetate and the least time in SPMS when receiving ocrelizumab, with teriflunomide and dimethyl fumarate being second and third, respectively. These results are consistent with the SPMS outputs directly from	

<table>
<tr><th>Comment number</th><th>Type of stakeholder</th><th>Organisation name</th><th>Stakeholder comment
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<tr><td></td><td></td><td></td><td>
the ponesimod model, where patients spent on average [redacted] of their time in SPMS, and the same order of time spent in SPMS based on treatment type i.e., spending the most time in SPMS when receiving glatiramer acetate, then dimethyl fumarate, then teriflunomide and the least when receiving ocrelizumab out of the four treatments.

Table 6 Time spent in SPMS stated in ponesimod and peginterferon model

<table>
<tr><th>Treatment</th><th>% Time spent in SPMS (Janssen base case analysis a)</th><th>% Time spent in SPMS (Janssen model with Peg inputs b)</th><th>% Time spent in SPMS (peginterferon model c)</th><th>Difference (column b – column c)</th></tr>
<tr><td>Teriflunomide</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Dimethyl Fumarate</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Glatiramer Acetate</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Ocrelizumab</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
</table>

We conducted additional scenario analysis, which replaced the peginterferon input data with the data in the ponesimod model in order to test whether the ponesimod model could replicate the time spent in SPMS stated in the peginterferon submission. We were able to retrieve most inputs from the peginterferon submission except for the company’s own NMA analysis. Due to this, some variation was expected, but we saw that the ordering of highest to lowest time spent in SPMS did not change i.e., teriflunomide, dimethyl fumarate, glatiramer acetate and ocrelizumab. In addition, the results were relatively consistent with the outputs noted in the peginterferon model itself. Therefore, it could be concluded that the ponesimod model is highly aligned to the peginterferon model results for time spent in SPMS.
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</table>

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			Please note that the scenario analysis was based on the pooled interferon class-based NMA model and not on updates using the hierarchical class-based NMA results. We note, that since the Committee/ERG updated the hazard ratios (HR) to relative risks (RR) this is part of the model engine and results have been calculated on risk ratios and not hazards, due to this version being presented at ACM 1. Although the change from HR to RR does not have a significant impact to the model outputs, there is a small difference in QALYs, where QALYs are greater with HR over RR, so the change implemented by the ERG/Committee has reduced the QALY's slightly. Overall, the outputs for time spent in SPMS are broadly consistent between ponesimod and peginterferon, we have validated the ponesimod model structure and ensured that there are no errors in the model causing unreliable or unpredictable outputs. In addition, the models QALY estimates are related to time spent in SPMS states, since patients with SPMS will clinically have a lower utility and will therefore likely progress to later disease stages, which in turn also has lower utility values associated. As requested by the Committee, several changes have been made to the model to produce a new base case model. The updated changes and their impact on the model outputs and time spent in SPMS are discussed in comment 4.1 – 4.4 However, we would like to note here, that the inclusion of mortality from the Harding et al 2018 source as opposed to Pokorski, 1997 source, results in increased QALY outputs and hence a more even split of patient time spent in RRMS and SPMS states.	
29	Consultee	Janssen-Cilag	**Comment 4.1. Results of new base case economic model: the overall cost-effectiveness of the economic model remains the same in the revised economic model i.e., ponesimod is a cost-effective treatment option for patients with active and highly active RRMS** **(ACD 3.10 – page 11)**	Thank you for your comment; it was considered during decision making.

<table>
<tr><th>Comment number</th><th>Type of stakeholder</th><th>Organisation name</th><th>Stakeholder comment
Please insert each new comment in a new row</th><th>NICE Response
Please respond to each comment</th></tr>
<tr><td></td><td></td><td></td><td>
The new base-case model assumes the following key inputs:
<table>
<tr><th>Input</th><th>Pooled NMA economic model inputs (presented at ACM 1)</th><th>Revised model updated during ACD</th></tr>
<tr><td>NMA</td><td>Based on the pooled class-based interferon NMA</td><td>Hierarchical class-based interferon NMA</td></tr>
<tr><td>Mortality</td><td>Pokorski, 1997</td><td>Harding et al 2018 (with Pokorski, 1997 data for EDSS states 0 – 3)</td></tr>
<tr><td>Annual conversion probability from RRMS to SPMS</td><td>Mauskopf, et al., 2016</td><td>ERG revision of Mauskopf, et al., 2016 from peginterferon submission</td></tr>
<tr><td>Transition probability matrices</td><td>Janssen model HR in line with previous models in MS. ERG made a switch upon Committee lead team request prior to committee meeting to convert HRs to RRs</td><td>Revised model keeps the RR switch</td></tr>
</table>
Overall, with the revised model inputs there is minimal change in cost-effectiveness estimates in the hierarchical class-based NMA relative to the pooled interferon class NMA. This denotes that the two NMAs are aligned.

Results of the economic model with the hierarchical class-based NMA result in the following: in active RRMS, ponesimod is cost effective and is dominating (i.e., higher clinical outcomes and cost saving) teriflunomide, dimethyl fumarate,
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</table>

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			glatiramer acetate, the interferon class (and ozanimod) which are all first line treatments in RRMS. Ocrelizumab and ofatumumab were more costly and more effective than ponesimod as monoclonal antibody treatments. However, this could still be seen as a cost-effective use of resources. It is also important to note that neither ocrelizumab or ofatumumab are orally administered, requiring administration either by intravenous infusion or via subcutaneous injection, respectively, and so patients who are considering them as treatment options, will likely not be the same patients who are considering an oral DMT such as ponesimod. Furthermore, oral treatments are generally preferred by patients. It is important to note that the cost-effectiveness of the deterministic and probabilistic results for the active RRMS population align to the cost-effectiveness results presented in the economic model using the pooled interferon NMA. In highly active RRMS, again the conclusions that can be inferred are the same between the pooled NMA and Pokorski, 1997 mortality data and the hierarchical NMA and Harding, et al., 2018 source of data. Ponesimod dominates fingolimod, is less effective and less costly than ocrelizumab and alemtuzumab and is dominated by cladribine. It is important to note however that the Committee recognised that cladribine has a substantially higher treatment effect, in particular for 6-month disability progression, which is not supported by clinical practice, as noted by the clinical experts during the committee meeting.	
30	Consultee	Janssen-Cilag	**Comment 4.2 Deterministic and probabilistic results for the ITT RRMS population** The probabilistic results have been run based on 10,000 iterations of the economic model. We note that the probabilistic results are consistent with the deterministic results and indicate that ponesimod is a cost-effective treatment in first line RRMS. **Table 7 CEM base-case results for the ITT population**	Thank you for providing this cost effectiveness analysis for the Committee; it was considered during decision making.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment

Cost-Effectiveness Outcomes	Total Costs				Total QALYs				ICER per QALY (Probabilistic)	
	Mean (Probabilistic)	95% CI lower	95% CI upper	Deterministic (base case)	Mean (Probabilistic)	95% CI lower	95% CI upper	Deterministic (base case)		
Ponesimod 20mg PO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	–	–
Teriflunomide 14mg PO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominates	Dominates
DMF 240mg PO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominates	Dominates
GA 20mg SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominates	Dominates
IFN class	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominates	Dominates
Ocrelizumab 600mg IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Less Effective and Less Costly	Less Effective and Less Costly
Ofatumumab 20mg SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Less Effective and Less Costly	Less Effective and Less Costly
Ozanimod 1.0mg PO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominates	Dominates

Figure 9 Cost-effectiveness scatter plot for ITT population

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			 **Figure 10 Cost effectiveness acceptability curve for the ITT population** 	

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<tr><th>Comment number</th><th>Type of stakeholder</th><th>Organisation name</th><th>Stakeholder comment
Please insert each new comment in a new row</th><th>NICE Response
Please respond to each comment</th></tr>
<tr><td>31</td><td>Consultee</td><td>Janssen-Cilag</td><td>

Comment 4.3: Deterministic and probabilistic results for the highly active RRMS population

The probabilistic results have been run based on 10,000 iterations of the economic model. We note that the probabilistic results are consistent with the deterministic results and indicate that ponesimod is a cost-effective treatment in highly active RRMS.

Table 8 CEM base-case results for the Highly Active population

Cost-Effectiveness Outcomes	Total Costs				Total QALYs					
	Mean (Probabilistic)	95% CI lower	95% CI upper	Deterministic (base case)	Mean (Probabilistic)	95% CI lower	95% CI upper	Deterministic (base case)		
Ponesimod 20mg PO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	–	–
Ocrelizumab 600mg IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Less Effective and Less Costly	Less Effective and Less Costly
Ofatumumab 20mg SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Less Effective and Less Costly	Less Effective and Less Costly
Ozanimod 1.0mg PO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominates	Dominates
Alemtuzumab 12mg IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Less Effective and Less Costly	Less Effective and Less Costly
Cladribine 3.5mg/kg PO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
Fingolimod 0.5mg PO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominates	Dominates

Figure 11 Cost-effectiveness scatter plot for Highly Active population

</td><td>Thank you for providing this cost effectiveness analysis for the Committee; it was considered during decision making with the additional consideration of confidential comparator patient access scheme prices.</td></tr>
</table>

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			 Figure 12 Cost effectiveness acceptability curve for the Highly Active population 	

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
32	Consultee	Janssen-Cilag	**Comment 4.4. SPMS and modelled outputs in new model: modelled outputs from the economic model using Harding et al and the hierarchical class-based NMA, produce outputs that the Committee would expect to see in line with current clinical practice (ACD 3.10 – page 11)** As discussed, in the results section (comment 4.1 - 5.3) the updated base case model includes new assumptions based on mortality inputs from Harding et al 2018, switch to peginterferon inputs (NICE, 2020) for annual conversion from RRMS to SPMS (previously updated by the ERG), HR updated to RR (updated by the Committee/ERG prior to ACM 1), and updated inputs via the hierarchical class-based NMA. In order to review what outputs the revised model produces compared to the model presented at ACM 1 we have undertaken a comparison exercise to review the outputs of the new model in terms of both the modelled QALY outputs and time spent in the SPMS state based on the revised inputs. Below we discuss the changes and results as presented in table 9 and 10: • The initial model reviewed at ACM 1 included the following inputs: 6-month CDA based on pooled interferon class-based NMA, Mauskopf, et al., 2016 conversion RRMS to SPMS, Pokorski, 1997 with interpolation for mortality and HR to RR as updated efficacy by Committee/ERG. • For the revised base case the model inputs are as follows: 6-month CDA based on hierarchical interferon class-based NMA excluding ADVANCE/INCOMIN; peginterferon (NICE, 2020) conversion for RRMS to SPMS, Harding et al 2018 for mortality and HR to RR as updated by Committee/ERG. **Table 9 Ponesimod QALY model output based on the model reviewed at ACM 1 and revised base case**	Thank you for your comment. It was considered during decision making.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment

Treatment	QALYs (Janssen ACM1 base case)	QALYs (Janssen revised base case)
Ponesimod	[redacted]	[redacted]
Teriflunomide	[redacted]	[redacted]
Dimethyl fumarate	[redacted]	[redacted]
Glatiramer acetate	[redacted]	[redacted]
Interferon class	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]
Ofatumumab	[redacted]	[redacted]

Overall, in the new model there is an increase in QALY outputs by approximately 1 QALY (or slightly more), these results are more closely aligned to the outputs the Committee anticipated to see. However, we note that the changes in inputs does not change the overall cost-effectiveness of the model.

Table 10 Ponesimod time spent in SPMS in the model reviewed at ACM 1 and revised base case

Treatment	% Time spent in SPMS (Janssen ACM1 base case)	% Time spent in SPMS (Janssen revised base case)	Difference
Ponesimod	[redacted]	[redacted]	[redacted]
Teriflunomide	[redacted]	[redacted]	[redacted]
DMF	[redacted]	[redacted]	[redacted]
GA 20	[redacted]	[redacted]	[redacted]

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			<table><tr><td>Interferon class</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td>Ocrelizumab</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td>Ofatumumab</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr></table> The update of inputs in the economic model has produced a more even split of time patients spend in RRMS and SPMS states. We believe this is likely due to the inclusion of revised mortality data since the mortality data includes a higher risk of death in higher EDSS states particularly states 7, 8, and 9. As demonstrated, the time spent in SPMS from the ponesimod model presented at ACM 1 is closely aligned to the results displayed in the peginterferon model (NICE, 2020). Pokorski, 1997 inputs have been utilised in the majority of previous appraisals. However, the new mortality data is likely more reflective of clinical practice and patients spending approximately equal time in RRMS and SPMS states. In conclusion, we consider the model inputs and outputs for the ponesimod model are appropriate and are reflective of the current expectations of MS treatments, in line with comments from the clinical experts.	
33	Consultee	Janssen-Cilag	**Comment 4.5 Scenario analysis of the pooled class-based NMA in the economic model and the hierarchical interferon class-based NMA in the economic model produce similar outputs and do not impact cost effectiveness. There is therefore consistency between the two economic models** In order to examine if the results of the economic model using the pooled interferon class NMA provided similar results to the hierarchical class-based NMA, we conducted a scenario analysis using key model assumptions but maintaining the pooled NMAs to run deterministic results. Both models used mortality data sourced from Harding, et al., 2018 and employed	Thank you for your comment. Committee conclusions relating the hierarchical interferon class-based NMA can be seen in section 3.10 of the FAD.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment

annual conversion probability of RRMS to SPMS from the peginterferon appraisal, in line with the ERG update. CDA progression was based on 6-month CDA and ponesimod was ran using the revised patient access scheme (PAS) price, while comparator disease modifying treatments (DMTs) were at their respective list prices.

Results for the intention-to-treat (ITT) population are presented in table 11 and results for the highly active population are presented in table 12. Overall, the total costs and QALYs are consistent across both models and are in harmony in terms of the conclusions that can be drawn.

Table 11 Scenario analysis of outputs from economic model using the pooled interferon class-based NMA vs hierarchical class-based interferon NMA for the ITT population

Treatment	Pooled interferon class-based NMA model			Hierarchical interferon-class based NM		
	Total Cost (discounted)	Total QALY (discounted)	Cost Effectiveness Conclusion	Total Cost (discounted)	Total QALY (discounted)	Cost Effectiveness Conclusion
Ponesimod 20mg PO	[redacted]	[redacted]	—	[redacted]	[redacted]	—
Teriflunomide 14mg PO	[redacted]	[redacted]	Ponesimod Dominates	[redacted]	[redacted]	Ponesimod Dominates
Dimethyl fumarate 240mg PO	[redacted]	[redacted]	Ponesimod Dominates	[redacted]	[redacted]	Ponesimod Dominates
Glatiramer acetate 20mg SC	[redacted]	[redacted]	Ponesimod Dominates	[redacted]	[redacted]	Ponesimod Dominates
Interferon	[redacted]	[redacted]	Ponesimod	[redacted]	[redacted]	Ponesimod

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment

class			Dominates			Dominates
Ocrelizumab 600mg IV	[redacted]	[redacted]	Less costly, Less Effective	[redacted]	[redacted]	Less costly, Less Effective
Ofatumumab 20mg SC	[redacted]	[redacted]	Less costly, Less Effective	[redacted]	[redacted]	Less costly, Less Effective
Ozanimod 1.0mg PO	[redacted]	[redacted]	Ponesimod Dominates	[redacted]	[redacted]	Ponesimod Dominates

Table 12 Scenario analysis of outputs from economic model using the pooled interferon class-based NMA vs hierarchical class-based interferon NMA for the Highly Active population

Treatment	Pooled interferon class-based NMA model			Hierarchical interferon class-based NMA		
	Total Cost (discounted)	Total QALY (discounted)	Cost Effectiveness Conclusion	Total Cost (discounted)	Total QALY (discounted)	Cost Effectiveness Conclusion
Ponesimod 20mg PO	[redacted]	[redacted]	—	[redacted]	[redacted]	—
Ocrelizumab 600mg IV	[redacted]	[redacted]	Less costly, Less Effective	[redacted]	[redacted]	Less costly, Less Effective
Ofatumumab 20mg SC	[redacted]	[redacted]	Less costly, Less Effective	[redacted]	[redacted]	Less costly, Less Effective
Ozanimod 1.0mg PO	[redacted]	[redacted]	Ponesimod Dominates	[redacted]	[redacted]	Ponesimod Dominates
Alemtuzumab 12mg IV	[redacted]	[redacted]	Less costly, Less	[redacted]	[redacted]	Less costly, Less

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			<table><tr><td></td><td></td><td></td><td>Effective</td><td></td><td></td><td>Effective</td></tr><tr><td>Cladribine 3.5mg/kg PO</td><td>[redacted]</td><td>[redacted]</td><td>Dominated</td><td>[redacted]</td><td>[redacted]</td><td>Dominated</td></tr><tr><td>Fingolimod 0.5mg PO</td><td>[redacted]</td><td>[redacted]</td><td>Ponesimod Dominates</td><td>[redacted]</td><td>[redacted]</td><td>Ponesimod Dominates</td></tr></table>	
34	Consultee	Janssen-Cilag	**Comment 5 Factual inaccuracy (ACD 3.2 – page 5): Ponesimod positioning** In the ACD, NICE noted that "*at technical engagement the company updated its positioning of ponesimod to exclude rapidly evolving severe disease*"; Janssen would like to highlight that ponesimod was always positioned in the active and highly active RRMS treatment lines, since clinical feedback (in line with Committee clinical expert agreement) was that ponesimod would be most beneficial to patients with active and highly active RRMS. This was reflected in our initial submission NMAs and model structure. However, during technical engagement the ERG asked for clarification on positioning since there was a small proportion of patients who could be considered to have Rapidly Evolving Severe (RES) RRMS in the phase 3 OPTIMUM trial in line with NHS England's treatment algorithm.	Thank you for your comment. This section has now been amended.
35	Consultee	Janssen-Cilag	**Comment 6 Misleading statement (ACD 3.4 – page 7): Disability accumulation** In the ACD, NICE highlights that "*OPTIMUM showed a statistically significant difference in annualised relapse rate and change in fatigue-related symptoms for ponesimod compared with teriflunomide. The committee considered the differences seen in 3- and 6-month confirmed disability accumulation were uncertain*". In the phase 3 OPTIMUM trial, the risk for 3-month and 6-month CDA for ponesimod 20 mg compared to teriflunomide 14 mg was estimated to be 17% and 16% lower, respectively, which is consistent between CDA outcomes. Furthermore, the study was not powered to show superiority between the measures (Kappos, et al., 2021). The outcomes of the trial are very much in line with previous trials in MS and we	Thank you for your comment. Section 3.4 of the FAD refers to the OPTIMUM trial and does not discuss any of the NMAs conducted as part of the appraisal.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			therefore believe this statement to be misleading to the public, as it implies there may be issues with disability outcomes or trial results. If, however NICE are referring to the difference in results seen between the economic model outputs when employing either the 3-month or 6-month CDA, we believe this should have been clearly stated. It is not uncommon to see differences in results from the economic models between 3-month and 6-month disability since the models are driven by NMAs which utilise the entirety of MS data from other company comparator drug trials; as noted in the ponesimod appraisal and during the majority of MS appraisals there is heterogeneity across MS trials in general due to the different populations, outpoints collected, duration of trials conducted, and how recently the trials were conducted. This is not a special situation in the appraisal of ponesimod, since the Committee have seen this issue across all MS appraisals over the years. In recent MS appraisals the themes of heterogeneity between MS trials have always been a discussion point and was discussed to some degree in the appraisals of ofatumumab (TA699) (NICE, 2021), peginterferon (TA624) (NICE, 2020) and ocrelizumab (TA533) (NICE, 2018). However, for each appraisal the Committee were able to make an informed decision and conclude on each treatment's clinical effectiveness. The evidence presented for ponesimod is no different.	
36	Consultee	Janssen-Cilag	**Comment 7 Factual inaccuracy (ACD 3.7 – page 9): Network meta-analyses** In section 3.7 NICE notes that "*to reduce heterogeneity in study design, at technical engagement the company suggested pooling interferons*". We would like to clarify that at technical engagement the heterogeneity and clinically implausible results produced by some of the interferon trials (namely INCOMIN and ADVANCE) were discussed with the ERG, and the suggestion to conduct a pooled interferon NMA came from the ERG. In line with this suggestion Janssen carried out a class-based NMA as the revised base-case for ACM 1.	Thank you for your comment. This section has now been amended to reflect this.
37	Consultee	Janssen-Cilag	**Comment 8 Additional Comment (ACD 3.9 – page 10): Cladribine in highly active RRMS**	Thank you, this comment has been noted. Further information relating to cladribine can be

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			In section 3.9 if the ACD, NICE notes "*cladribine had a substantially higher treatment effect for 6-month confirmed disability accumulation than other treatments in the network meta-analysis for the highly active subgroup. It noted that this estimate had wide credible intervals, indicating a high level of uncertainty. The committee noted that because 6-month confirmed disability accumulation is a key driver of the model, this estimate also had a large impact on the cost-effectiveness estimate of cladribine*". We wanted to reiterate that there is uncertainty in the clinical data for cladribine and in addition, highlight that in the treatment of highly active RRMS induction treatments such as cladribine will not be the most appropriate comparator to ponesimod as it will most likely be fingolimod.	found in section 3.9 of the FAD.
38	Consultee	Janssen-Cilag	**Comment 9 Clarification (ACD 3.10 – page 11): Methodology of pooled NMA** In the ACD, NICE notes "*It also understood that the company had excluded several trials that compared interferons with each other from the pooled network*" – Janssen would like to clarify that the interferon vs interferon trials were not excluded by Janssen out of choice, but instead because it was not possible, methodologically to incorporate interferon vs interferon trials since they did not provide any comparative data.	Thank you, this comment has been noted.
39	Consultee	Janssen-Cilag	**Comment 10 Clarification (ACD 3.11 – page 12): Evidence of serious and rare adverse events** In the ACD, NICE discuss that "*the committee considered that further data would be needed to fully establish ponesimod's safety profile*". Janssen would like to reiterate the availability of up to 10-years' worth of data for ponesimod from the phase 2 trial and that the phase 3 study is over 2-years long (108 weeks) which is a significant amount of data for a new MS DMT. In comparison to other DMTs which were appraised by NICE, the ponesimod trials report some of the longest safety data presented to a Committee, when the Committee have always previously been able to recommend comparator treatments.	Thank you, this comment has been noted.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
40	Consultee	Janssen-Cilag	**Comment 11 Clarification (ACD 3.12 – page 13): Long-term efficacy** In section 3.12, NICE discuss that, "*the committee considered that longer-term efficacy is difficult to establish and extrapolate from short-term trials used in the network meta-analyses, the outputs of which have broad credible intervals*". We appreciate that there are challenges in the data for MS, however we would like to highlight again the network data and trials being reviewed by the Committee are no different for ponesimod, than for other previous appraisals. Just this year (2021) the NICE Committee met to conclude on the appraisals of ofatumumab (NICE, 2021) and ozanimod (NICE, 2021). Furthermore, we would like to reiterate the long-term phase 2 data that is available for ponesimod, in addition to over 2 years of phase 3 data.	Thank you, this comment has been noted.
41	Consultee	Janssen-Cilag	**Comment 12 Factual inaccuracy (ACD 3.15 – page 15): Treatment sequencing for SPMS** In section 3.15, NICE note that "*the company did not present any analysis that allowed for treatment switching or sequencing*". Janssen would like to clarify that for the original submission we accounted for sensitivity analysis in the model, which allowed active RRMS patients to move onto one treatment (cladribine) and similarly patients with highly active disease were allowed to move onto natalizumab. During technical engagement, the ERG noted that this was a "*simplifying approach*" and that "*modelling subsequent treatment effects introduced additional uncertainty*". While we appreciate the rationale stated by the ERG during technical engagement and understand in line with Committee comment that "*an economic model that can simulate treatment sequencing would be complex to construct*", we note that we did indeed attempt to factor treatment sequencing into the economic model to allow for a more realistic treatment follow-on. However, as already stated by the clinical experts the subsequent treatments which patients receive is usually determined by the treatment they are currently on in addition to several individualised factors, making treatment sequencing in the model highly complex.	Thank you for your comment. This section has now been amended.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
42	Web		Has all of the relevant evidence been taken into account? Yes Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? Not sure Are the recommendations sound and a suitable basis for guidance to the NHS? No 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? Not that I can see General comments: "To whom it may concern Re: Ponesimod drug trial - Janssen I have heard today that NICE does not recommend Ponesimod (Ponvory) as an NHS treatment in England and Wales and have been asked to write, as a participant in this drug trial since 2010, to share my experience. I understand that there are only 13 UK participants and that the average results have been extremely good. My personal experience has been exceptional. In the year before starting the drug I suffered drop foot, double vision, numbness on my face and severe fatigue. I started the drug a few months after my last relapse and haven't had a relapse since… that's 11 years!! Your argument against the drug is that you are 'unsure of Ponesimod's ability to slow down disability progression' and therefore, 'ponesimod is not considered to be cost-effective for the NHS'. This has been an 11 year trial and for me to have no	Thank you for your comment. The committee considered all evidence submitted. The views of clinical experts and patient/carer representatives were considered by the Committee when formulating its recommendations. Ponesimod is now recommended in the FAD.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			relapses is incredible. I do not need to claim disability benefits because of the effectiveness of this drug. When reading through your paper for approving Fingolimod (Gilenya) you said '94.1% of all patients treated with fingolimod had no disability progression after 3 months'. This trial has been 11 years and could surely show how much disability progression there has/has not been, thankfully none in my case. I look to my future and obviously consider that my condition may worsen but hope that I; do not lose my voice, my mobility or my sight to name but a few devastating effects that this disease can bring. I truly believe that Ponesimod has been the reason for my continuing good health. What price does NICE place on the quality of life of someone with MS? Participants have selflessly for the last 11 years given their time for hundreds of hospital appointments in the hope that they may make a difference to the lives of others with RRMS in the future? Every bit of feedback I have had about this drug has been nothing but positive and I will be devastated if it isn't approved. As a footnote I have also noticed that The European Commission has approved Ponesimod (Ponvory) which makes me feel even more sad. Kindest regards. [redacted]	
43	Web		<u>Has all of the relevant evidence been taken into account?</u> "The UKMSSNA would like NICE to take into account the Pharmacokinetics of Ponesimod and its affect on Multiple Sclerosis Patients. Ponesimod has a short half-life and therefore unlike some other treatments for Multiple Sclerosis it is eliminated from the body quickly and the bodies normal immune response can return within seven to eight days. This is beneficial for several situations such as a patient wanting to start a family, change to another medication or if the patient has other health problems. Ponesimod has no active metabolites this means that it has less interactions with other medications. Patients with Multiple Sclerosis are often on medications to control their symptoms and due to the younger cohort of	Thank you for your comment. The committee considered all evidence submitted. The views of clinical experts and patient/carer representatives were considered by the Committee when formulating its recommendations. Ponesimod is now recommended in the FAD.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			patients may also be taking medication for contraception. The UKMSSNA feels that because of the cohort of patients that Multiple Sclerosis affects (younger adults) these are benefit of Ponesimod that other disease modifying therapies do not have and these benefit are desirable for patients who wish to have control over their treatment and life. The UKMSSNA would like NICE to consider the effects of Fatigue on Multiple Sclerosis Patients. Ponesimod is the first disease modifying therapy to show data that suggests a statistically significant reduction in fatigue levels. The UKMSSNA would like NICE to acknowledge that fatigue is a disabling factor in Multiple Sclerosis suffers. Studies suggest fatigue affects 75-85% of Multiple Sclerosis patients and has a detrimental effect to their psychosocial and physical wellbeing. Fatigue is a common factor in Multiple Sclerosis that is not related to the severity of the disease. Fatigue has a serious implication for a population of patients that are of working age which has a direct financial impact on the individual and the state. There are very limited methods and medications used to manage fatigue. The medications that are available to assist with fatigue are off licence and have poor efficacy and poor data to support their use. Fatigue management programmes or psychological therapies often have long waiting lists or are only available in certain areas of the country. The UKMSSNA welcomes any medication that could reduce this disabling factor of Multiple Sclerosis and feels that Ponesimod has a dual purpose in the management of Relapsing remitting Multiple Sclerosis. <u>Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?</u> The UKMSSNA would like to argue that Ponesimod has shown efficacy and safety in trials and that if the cost was to be within a price range that NICE found acceptable Ponesimod would offer Multiple Sclerosis suffers a first line oral medication. Ponesimod could improve adherence due to the nature of how this medication is taken compared to other first line competitors and would give patients more choice. Research has shown the importance of early treatment in Multiple Sclerosis to reduce the progression of the disease process and prevent disability. As Multiple Sclerosis advances and disability increases so does the cost to the state and to the individual in terms of care needs, financial cost, inability to work,	

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			care givers needs and psychosocial wellbeing of the patient and their family (supporting studies can be supplied to NICE if required). The UKMSSNA believes that starting treatment earlier in the disease course reduces the overall cost of Multiple Sclerosis to the individual and the state. The UKMSSNA accept that there was no significant statistical difference shown in disease progression between Ponesimod and Teriflunomide, but would like NICE to appreciate that it is difficult to gain data on disability progression in such a short period of time. It is possible that changes in the Expanded Disability Status Score (EDSS) at either of these end points (12 weeks and 24 weeks) could be due to a relapse rather than disease progression. Teriflunomide has been licenced for Relapsing Remitting Multiple Sclerosis since 2014. Since licencing Teriflunomide has proven its efficacy with post marketing real world data, there are a number of studies that reflect this (can be presented to NICE if required). Ponesimod had similar efficacy to Teriflunomide in disease progression in the trial OPTIMUM, this would indicate that it is likely to have a similar outcome in the real world. Another indication of this is that Ponesimod showed in the OPTIMUM trial that it reduced annual relapse rate by 30.5% compared to Teriflunomide and active or new lesions by 56%. Compared to Teriflunomide. A reduction in lesion load or active lesions would suggest a reduction in disease progression and disability. <u>Are the recommendations sound and a suitable basis for guidance to the NHS?</u> No The UKMSSNA would argue that Ponesimod has a number of factors that would make it beneficial as a first line treatment for people with Relapsing Remitting Multiple Sclerosis. UKMSSNA would urge NICE to reconsider Ponesimod as a first line treatment of Relapsing Remitting Multiple Sclerosis 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? No	

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
44	Web		Has all of the relevant evidence been taken into account? I am a patient who has been on Ponvory, formerly Ponesimod, and formerly ACT 128800, for the last 12 years. I am a 45 year old man, married with 2 boys. In the time I have been on the medication, I have ran several half marathons and one whole marathon, in less that 4 hours. I receive treatment through BRAMS in Bristol. I was newly diagnosed 12 years ago, with mainly sensory symptoms, and a record of an increasing number of relapses in the preceding 24 months, which had an increasing amount of pain and discomfort, including one episode of particularly painful optical neuritis. I entered the trial within 6 months of diagnosis. I have had 12 years of no further relapses, and in addition, any symptoms at the start have disappeared. I have no side effects to the medication. While I am not technically cured, I live my life every day with no restriction whatsoever. I feel as though I am cured. I work full-time in a global technology company. I have had no days off sick due to MS ever. This is a remarkable medication, and while every decision has to have a cost-benefit analysis, if you ever wanted a walking advert for this medication, it's me. It is so easy to administer as an oral drug, there are no noticeable side effects. Ponvory would introduce a powerful new weapon in the armoury against MS, against people losing their mobility, and taking sick leave, and forcing them into permanent sick pay, housing benefit and other costs to the state. I do not claim any benefits, and contribute a large amount of tax every year. This should be part of your evidence. If you want a case study i am at [redacted] The medication should be the default medication as a first line defence against MS	Thank you for your comment. The committee considered all evidence submitted. The views of clinical experts and patient/carer representatives were considered by the Committee when formulating its recommendations. Ponesimod is now recommended in the FAD.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? No. I believe there are only a very small number of people on this medication in the UK, and I know most, if not all, of them through BRAMS in Bristol. We are all fantastic adverts for this medication allowing us to continue working, paying taxes, living life, and not claiming disability allowance. Are the recommendations sound and a suitable basis for guidance to the NHS? Without knowing the price of the drug which is confidential, and without knowing how it compares to other medications in price, this is hard to answer. 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? No	
45	Web		Has all of the relevant evidence been taken into account? It feels that the consultation has been aimed more at clinicians rather than participants who may have wished too be more actively involved. I also feel that the cognitive side of MS was not taken into consideration in the research. I would like to state that on average my cognitive health has remained good and I believe this is a result off taking Ponesimod. Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? I am not an analyst, but a patient with RRMS. as far as I am concerned as previously stated in comments the opportunity cost of potential care for someone later in life wit RRMS has to be balanced against the cost of the life changing drug	Thank you for your comment. The committee considered all evidence submitted. The views of clinical experts and patient/carer representatives were considered by the Committee when formulating its recommendations. Ponesimod is now recommended in the FAD.

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			that could keep them fit and healthy for longer. These are abstract and indeterminate factors as none of us know that course and pathway of our future but the evidence of being on the drug for me for 11 years is that I consider myself to be fairly fit and well having been diagnosed for this length of time and I have quality of life. Why would I want this potentially to change by being denied this drug in the future> <u>Are the recommendations sound and a suitable basis for guidance to the NHS?</u> No the recommendations are not sound. Treatments for RRMS..my experience on Ponesimod is that the number of relapses reduced to zero when I started taking the drug 11 years ago, I believe the progression of my disability has been kept to the minimum and I have a good quality of life. My MS does not prevent me doing something I want to do. I do have to manage my condition and take responsibility for my own symptoms such as eating healthily and exercising sensibly and resting if my body demands it, but I believe that Ponesimod plays a significant part in extending my mobility and future quality of life. What measures are used in terms of time for short term and long term as I could not see this stated in the consultation document (apologies if I have missed this) How long would 11 years be considered in view of the outcome measures and analysis of results? What is ""AN ACCEPTABLE USE OF NHS RESOURCES"" How much is my life worth? How do you measure clinical evidence and benefit against short term evidence if you have not even listened to the personal experiences of drug trial participants. It is not all about looking at brain scans and EDSS scores. I am a strong advocate for Ponesimod if this has not been previously picked up and believe that my own personal experience counts and hope that as a disabled person, my voice will be listened to and heard. <u>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?</u> I am less concerned about this aspect of the consultation and do not particularly feel that there has been discrimination. The only point I would make is that as	

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			someone with the disability of MS, I would like to feel certain that my viewpoints have been taken into account in the final recommendations and I hope that the initial decision will be overturned. <u>General comments</u> Treatments for relapsing multiple sclerosis include many disease-modifying treatments. These aim to reduce the number of relapses, slow the progression of disability, and maintain or improve quality of life. Clinical trial evidence shows that ponesimod reduces the number of relapses compared with teriflunomide. However, ponesimod's effect on disability progression is unclear. Comparisons with other disease-modifying treatments are limited by uncertainties in the clinical evidence. My experience of disability progression is that I have remained stable in terms of my RRMS since I started taking the drug and it has enabled me to have a quality of life I did not think was possible. My EDSS score has remained low ..between 1-3 I believe for 11 years. How long does NICE consider long term progression to be...11 years of being on the drug is in my humble opinion quite a long time of my life. What dies NICE consider an acceptable use of resources. Spending money on a drug that potentially changes lives of someone with RRMS, or spending money on their future care because they have been denied the drug that could help them. These opportunity costs could include physio, OT, personal care, nursing, neurology, MRI scans, mental health services. Ponesimod is a life changer for someone with RRMS..I know and it has helped me immensely. Ponesimod is not recommended, within its marketing authorisation, for treating relapsing forms of multiple sclerosis with active disease defined by clinical or imaging features in adults. I have been a participant on the Ponesimod drug trial and was diagnosed with RRMS in 2010 and it has been life changing as have had no relapses since my original two in 2010. This recommendation is not intended to affect treatment with ponesimod that was	

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			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. My treatment on Ponesimod has been paid for by drug trial company Janssen so what happens to a participant who has given up 11 years of their life to hundreds of appointments to hopefully help others in the same way I have been helped. Who will fund my future treatment? Multiple sclerosis is a chronic, lifelong disease with no cure, resulting in progressive, irreversible disability. It has many symptoms, including pain, chronic fatigue, unsteady gait, muscle loss, speech problems, incontinence, visual disturbance and cognitive impairment. Most people have the relapsing–remitting form of the disease, characterised by periods of new or worsened symptoms. The patient experts highlighted that the disease is complex and unpredictable and impacts all aspects of life and can affect carers too. The disease has a higher prevalence in women. Because it is typically diagnosed when people may be thinking about having children, the patient experts highlighted it is important to consider treatments that can be used during pregnancy. The company noted that although ponesimod is not indicated for pregnant women, its short half-life could be helpful for pregnancy planning compared with drugs with longer half-lives. The patient experts also highlighted that oral treatments are generally preferred and that ponesimod is an oral treatment. The committee concluded that despite many available treatments, people would welcome new treatment options for relapsing multiple sclerosis. Comment on section: Treatment pathway, population and comparators I believe that Ponesimod has been approved by the FDA and also in Europe as a treatment for RRMS, so it seems very unfair that patients in the UK, will be excluded from being offered Ponesimod as a result of BREXIT. An oral drug is easy to take and I believe that the average results of the 13 participants in the UK have been extremely encouraging for 11 years. It is important that NICE considers the personal experiences of participants as well as the clinical evidence. Yes the disease is unpredictable, different for each person and the disease can change in	

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			an instant. But all the more reason to try and prevent relapses to keep patients stable and relapse free. What cost does NICE place on people's quality of lives? The company measured fatigue symptoms using the Fatigue Symptoms and Impacts Questionnaire: Relapsing Multiple Sclerosis (FSIQ-RMS). It considered that OPTIMUM was the first trial to use a validated disease-specific fatigue measure as a prespecified endpoint and show a disease-modifying treatment can stabilise fatigue symptoms. The patient experts highlighted fatigue as an important element of quality of life and that some people would switch to a drug that was shown to act on fatigue. The clinical experts suggested that ponesimod may reduce inflammation which can reduce fatigue. The committee agreed that fatigue symptoms are an important element of the disease and that the FSIQ-RMS has potential to be an important disease outcome measure. However, fatigue was not explicitly included in the model and was instead captured through measuring health-related quality of life by EDSS score (see section 3.12). The committee also noted that because there was no evidence on fatigue symptoms from other clinical trials using the FSIQ-RMS, ponesimod could not be compared with drugs other than teriflunomide. The committee concluded that fatigue is an important outcome measure that was not explicitly modelled in the cost-effectiveness analysis. It was uncertain what effect fatigue would have on cost-effectiveness results without seeing data on how well the comparator treatments reduce fatigue. Comment on section: Network meta-analysis Fatigue is one of my most prevalent symptoms of MS as well as some paraesthesia, but since being on the drug, I strongly believe that my fatigue would have been far more severe, and that reduced inflammation has helped this as a result of Ponesimod. Fatigue is a subjective measure as we are all individuals so it is difficult to measure this fairly, but individual experience needs to be listened to. the EDSS does not in my opinion adequately measure fatigue and many of the questions on the scale are not particularly relevant to my MS. Fatigue for me includes such things as mild cognitive impairment, brain fog, slowing up in general activities and reduced ability to carry out normal day to day activities. I would state that it has usually been when I have had abnormal activities that my fatigue has been adversely affected such as when travelling abroad with a time difference (..that was before Covid-19 hit the world) when an unexpected stressful event	

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			happens and other such events such as bereavement or loss, which would make any normal person without a condition more likely to slow up in life. List to personal experiences from drug participants about their fatigue as perhaps not sufficient date. Ponesimod makes a massive difference. The committee considered further analysis was needed to understand the impact of uncertainty on the economic analysis. This would include: further summary statistics and sensitivity analysis on the network meta- analyses, and particularly for interferons: model fit statistics and analysis of inconsistency in the pooled analyses, including trials that compare different interferons with each other in the network, to make direct comparisons between different models possible (see 3.10)a hierarchical class-based model for the interferons, assuming individual treatment effects within a class come from a distribution of effects with a class mean and between treatment variance within class analysis using updated mortality assumptions informed from new evidence further sensitivity analysis that produces more likely modelled outputs, including rate of secondary progressive multiple sclerosis progression and explanation of any inconsistencies of modelled outputs with previous appraisals. If further analysis is required, then the best way of securing this data is for existing participants to be funded for further longer term research. You can follow me for the rest of my life if it will help me and others. I would not put my life at risk if I believed that there was a safety issue. I have three adult children and I want to be a grandmother who can actively enjoy her life at some point in the future. Please listen to participants and not just clinicians as some clinical observations are subjective and speaking personally I would like to think as someone who is considered to have a disability, that this disability does not rule my life. In my opinion Ponesimod holds the key to however long I may have left in this world. I am 58 and hope to live a long and fulfilled life. Surely NICE wants this for patients instead a life of immobility and misery? If further analysis is required then I would be happy to continue to be studied as a long term participant on drug trial	
46	Web		The document states ponesimod's effect on disability is unclear. I totally disagree with this statement. This medication has had a massive effect on my disability, as	Thank you for your comment. The committee considered all

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			my disability has not deteriorated at all in the 10 years that I have been taking this medication. Also I have had no relapses in this time either. I feel this medication has had a positive effect on my health and would benefit many other patients with M.S. It seems such a shame that other M.S sufferers will not have the opportunity to benefit from this drug.	evidence submitted. The views of clinical experts and patient/carer representatives were considered by the Committee when formulating its recommendations. Ponesimod is now recommended in the FAD.

NICE National Institute for Health and Care Excellence

Ponesimod for treating relapsing multiple sclerosis [ID1393]

	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):	Janssen Cilag. Ltd
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	NA
Name of commentator person completing form:	Sarah Richards

NICE National Institute for Health and Care Excellence

Ponesimod for treating relapsing multiple sclerosis [ID1393]

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 [redacted] and all information submitted under [redacted]. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with 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.

NICE National Institute for Health and Care Excellence

Ponesimod for treating relapsing multiple sclerosis [ID1393]

Janssen responses to the NICE Appraisal Consultation Document (ACD)
26 October 2021

Executive Summary

Janssen welcomes and thanks NICE for the opportunity to comment on the Appraisal Consultation Document (ACD) for ponesimod for treating relapsing multiple sclerosis [ID1393].

We agree with the Committee's view that people living with multiple sclerosis (MS) in England would welcome a new and convenient treatment option. We appreciate the Committee highlighting the unmet need and recognising that Janssen's economic model structure and inputs were in line with previous appraisals. As such, Janssen are disappointed with the preliminary decision not to recommend ponesimod. Janssen remains fully committed to addressing the Committee's comments and ensuring that people living with MS and their clinicians can access ponesimod.

We note that the Committee's decision not to recommended ponesimod is primarily due to the cost effectiveness estimates being uncertain based on limitations in the clinical evidence. We observe from the ACD that the uncertainty highlighted by the Committee stems largely from the comparative effectiveness estimates from the network meta-analyses (NMAs) and how the long-term benefit is predicted from the evidence.

We strongly disagree with the Committee's commentary that the comparative treatment effect for ponesimod is highly uncertain given the availability of up to 10-years' worth of data in the phase 2 trial and over 2-years' worth of direct head-to-head data vs teriflunomide in the phase 3 trial. We acknowledge that there is heterogeneity across trials in MS, which inherently leads to a degree of uncertainty in all NMAs presented in the submission but note this has also been present within previous NMAs considered in past NICE MS appraisals. This issue is therefore not unique to ponesimod and has been recognised in the past as a manageable concern in coming to positive decisions on new technologies in virtually all previous appraisals. Indeed, ahead of the first appraisal committee meeting (ACM), additional analyses to further address the uncertainty were conducted (beyond those previously required for decision making as suggested by the ERG); namely the pooled interferon class NMA. Further, in this response, we have taken onboard the Committee's preference for a hierarchical class-based model. Both the new interferon class hierarchical NMA and the pooled NMA (presented at ACM 1) demonstrate consistent results for the relative efficacy of ponesimod versus comparator treatments, which we hope should reassure the Committee regarding the comparative effectiveness uncertainties.

To address the uncertainty stemming from how the long-term benefit is predicted from the evidence (of which some trials are short-term), we have validated the model outcomes against previous appraisals to demonstrate that the model is consistent in its outputs. We have also updated the model with the additional mortality source that was identified in the first ACM and included the hierarchical class-based NMA in the model. When these changes are made to the model, we note that the outcomes are more in line with the Committee's expected outcomes mainly due to the changes in mortality source. The Committee should therefore have confidence that the model is appropriate for decision making and aligned to the expected benefit of MS treatments predicted by the evidence and the natural history of the disease.

NICE National Institute for Health and Care Excellence

Ponesimod for treating relapsing multiple sclerosis [ID1393]

Overall, as requested by the Committee we have provided further information in three key areas as highlighted in section 3.17 of the ACD:

1. Further summary statistics and sensitivity analysis of the NMAs including:
    a. Model fit statistics and analysis of inconsistency in the pooled analyses of the original company submitted NMA
    b. Submission of a hierarchical class-based NMA for interferons
2. Analysis using update mortality assumptions informed from new evidence
3. Further sensitivity analysis that produces more likely modelled outputs including rate of secondary progressive multiple sclerosis progression

The additional analyses reinforce that ponesimod is a clinically meaningful, convenient, and cost-effective treatment option for the management of MS. Furthermore, since the first ACM, we have revised the confidential patient access scheme (PAS), which further improves the cost-effectiveness of ponesimod and helps to support a positive recommendation for ponesimod as an option for people living with MS in England.

Below we have provided a short summary of the sections in the main response addressing the 3 main uncertainties as highlighted in the ACD, with overall conclusion of the Janssen response.

- **Section 1a: Summary statistics of the pooled interferon class-based NMAs, including model fit statistics and analysis of inconsistency demonstrate that the pooled NMA has good fit, and therefore is appropriate for decision making**

(Comment 1 -1.2) The results from the model fit statistics and analysis of inconsistency indicate that the pooled interferon class-based NMA presented at ACM 1 was appropriate and that there were no major concerns with the results produced. The overall conclusion of the results is that the pooled NMAs did not violate the consistency assumption required for NMA models, and therefore could be deemed acceptable to base decisions on. We believe that this NMA was reasonable and does not raise major concerns.

- **Section 1 b: An updated NMA based on a hierarchical class demonstrated consistency of results with the original pooled NMA**

(Comment 1.3 – 1.5) The Committee noted they would prefer to see the results of the pooled interferon class-based NMA as a hierarchical class-based NMA model. Hierarchical models can be useful, but one core assumption is that trials within a hierarchical model can be deemed as exchangeable. Due to known issues with some of the interferon trials, (e.g., that their results demonstrate they are more effective than suggested by clinical experience and further data), we excluded two outlier trials ADVANCE (Calabresi, et al., 2014) and INCOMIN (Durelli, et al., 2002) in line with methods employed in both the ofatumumab appraisal (TA699) (NICE, 2021) and from discussion in the ocrelizumab appraisal (TA533) (NICE, 2018). Overall, the cost-effectiveness results of the hierarchical class-based NMA when input into the economic model are consistent with the results from the pooled NMA. This means that there is reassurance in the results of both NMAs given they indicate the same overall conclusions.

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- **Section 2: Revision of mortality data in the model sourced from Harding, et al., 2018, where previously Pokorski, 1997 was the main source, better reflects current clinical practice, due to mortality values from the new study representing mortality of patients seen in current UK clinical practice**

(Comment 2.1) In line with the majority of appraisals in MS and past NICE Committee's preferred inputs, the economic model for ponesimod included mortality data sourced from (Pokorski, 1997). However, during ACM1 it was noted that the Committee would like to ascertain what model results would be produced by incorporating a recent mortality study in MS, since the study may better reflect current clinical practice, i.e., improved patient care, and better MS symptom management in recent years. To fulfil this request, we used the suggested Harding, et al., 2018 mortality data to update the assumptions for expanded disability status scale (EDSS) states 4 – 9. The new data source did not detail mortality data for EDSS states 0 - 3, and so Pokorski, 1997 remained as an input source for the lower EDSS states. This revised mortality data has been used in the new company base case.

- **Section 3: The QALY outputs produced by the ponesimod model for patients and the rate of time spent in RRMS and SPMS states is consistent with previous other models accepted by NICE in multiple sclerosis**

(Comment 3.1 - 3.2) We reviewed the QALY outputs and time spent in relapsing remitting multiple sclerosis (RRMS) and secondary progressive multiple sclerosis (SPMS) for ponesimod and compared this to recent NICE appraisals where information was available and unredacted. After a detailed examination of both requirements, we observed that the ponesimod model (based on the interferon class-based pooled NMA) produces similar QALY outputs to the recent appraisals of ofatumumab (TA699) (NICE, 2021) and peginterferon (TA624) (NICE, 2020), but that the QALY outputs for the multiple technology appraisal (MTA) of beta interferons and glatiramer acetate (TA527) (NICE, 2018) are unusually high (generally 2 to 3 times higher than in other appraisals). Furthermore, the time patients spent in the SPMS state in the ponesimod model is comparable to time spent in SPMS in the peginterferon appraisal model (TA624) (NICE, 2020). Both explorations provide validity that the modelling approach undertaken and outputs for ponesimod is appropriate and consistent with appraisals previously accepted by the NICE Committee.

- **Section 4: The hierarchical class-based model and updated mortality data produce outputs in the cost effectiveness model in line with changes in MS treatment that the Committee expected to see in ACM 1. The updated economic model is likely to better reflect current clinical practice, due to mortality values from the new study representing mortality of patients seen in current UK clinical practice and overall, the model demonstrates that ponesimod is a cost-effective option for MS.**

(Comment 4.1 – 4.5) The cost-effectiveness model was re-run using the updated mortality data as well as the efficacy inputs from the hierarchical class-based NMA. The results remained consistent with the results presented for the model using the pooled class-based interferon NMA; ponesimod dominates most treatments in active RRMS and is a less costly and less effective treatment option than the monoclonal antibody treatments in both active and highly active RRMS. In highly active RRMS the results also remained consistent and ponesimod was a dominant treatment to fingolimod. Ponesimod was dominated in comparison to cladribine. Although in relation to cladribine it is important to note that it is an induction therapy and may be used differently to ponesimod. Furthermore, the high treatment effect

in the cladribine trial (as noted by the clinical experts during ACM 1) is not consistent with clinical expectation, given it is no better than existing DMTs. It is important to note that the model results use the list price of comparator disease modifying treatments (DMTs). We note, however, that ponesimod remains a cost-effective treatment option in the management of MS and with the revision of the PAS price, we believe ponesimod is a cost-effective treatment, even when confidential comparator PAS prices are taken into account.

- **Section 5: Additional comments from the ACD and factual inaccuracies**

In section 5, we present minor comments such as factual inaccuracies from the ACD and points of clarification. Section 5 responses are presented in comments 5 – 13.

Overall conclusion

The additional evidence presented, suggests that both the pooled NMA model, and the revised hierarchical class-based NMA model are feasible options for decision making. Comparisons to previous MS NICE appraisals demonstrate that the model is consistent and reliable for decision making. The economic model also generates outputs aligned to Committee expectations based on the short-term clinical data and current clinical practice of MS in England.

Both the pooled and hierarchical class-based NMAs attempt to address some of the widely acknowledged uncertainty within the interferon studies. We provide the hierarchical class-based NMA in the economic model (with updated mortality inputs) as the new base-case. However, we also provided the Committee with an alternative scenario using the economic model with the pooled interferon class-based NMA (with updated mortality inputs) for their consideration as well.

It is important to note the place of interferons within the current clinical landscape with regards to decision making. Interferon treatments are no longer widely used in clinical practice (for new patients) and are mostly reserved for patients already receiving them, which means this is an important point for decision making as opportunity cost is driven by therapies that will be displaced. Therefore, unnecessary weight should not be given to the use of interferon treatments as first line treatments, as the most relevant comparator to ponesimod in highly active RRMS will likely be moderate efficacy DMTs and oral treatments such as teriflunomide and dimethyl fumarate. This was confirmed by the four clinical experts we consulted during technical engagement, who noted that interferons are rarely used and would only be used in new patients for reasons such as they have a concurrent malignancy, occurrence of recurrent flu-like symptoms, patients' preferences not wanting to self-inject, and a higher incidence of skin reactions. Additionally, in the experts' practice peginterferon has been associated with neutropenia which has subsequently limited its use. We ask the Committee to also consider this wider context in their decision making.

The hierarchical class-based model predominantly impacts treatment for active RRMS where interferon treatments are positioned in England. However, both pooled and hierarchal class-based NMAs allow for decision making in highly active RRMS, where ponesimod could provide an alternative treatment option to DMTs such as fingolimod. For highly active disease the clinical experts noted that cladribine showed a greater treatment effect (based on 6-month CDA) in comparison to other DMTs available, but that this is not clinically plausible since it has similar efficacy to current treatments. We would agree with this

assessment but were unable to determine the rationale for the higher treatment effect in the cladribine trial.

We consider that overall, ponesimod is a beneficial and cost-effective treatment option to patients with active and highly active RRMS, especially since there is currently no treatment option with a sphingosine-1-phosphate (S1P) mechanism of action available in active RRMS. Furthermore, ponesimod would provide a convenient alternative to treatments in highly active RRMS, especially fingolimod, another S1P treatment.

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Section 1a: Summary statistics of the pooled interferon class-based NMAs, including model fit statistics and analysis of inconsistency demonstrate that the pooled NMA has good fit, and therefore is an appropriate tool for decision making (comments 1.1 – 1.2)

During technical engagement the Evidence Review Group (ERG) noted heterogeneity in the original ponesimod NMA due to varying treatment effects from interferon studies (each interferon was treated as a separate treatment in the original analysis). To overcome this, the ERG suggested a class-based NMA for the interferons may appropriately help to overcome this issue. NMAs were therefore conducted where all interferon regimens were pooled as a single treatment in the evidence networks. However, the Committee noted that it would like to review goodness-of-fit statistics and inconsistency assessments for the NMA of pooled interferons. Below we present both the model fit statistics and analysis of inconsistency for the pooled interferon class-based NMA.

Comment 1.1. The pooled interferon class-based model had good fit and is appropriate for decision making. (ACD 3.10 – page 11)

As requested by the Committee, the model fit statistics for the pooled interferon class-based NMAs are provided in table 1. It was not possible to incorporate the results of trials which compared interferon vs interferon in these analyses i.e., where the only eligible interventions were interferon regimens, given that such trials did not provide comparative data between interferon and another regimen of interest, and thus could not be included in a network in which all interferons were pooled in a single node. This resulted in 4 trials being excluded: EVIDENCE (Panitch, et al., 2002), INCOMIN (Durelli, et al., 2002), Mokhber, et al., 2015., and REFORMS (Singer, et al., 2012) trials.

Random vs. fixed effects models were selected based on best fit i.e., a lower deviance information criterion (DIC) value, and inconsistency analyses were performed considering only the model with better fit. For annualised relapse rate (ARR), and 3-month and 6-month confirmed disability accumulation (CDA) the fixed effect model produced the best fit, whereas for treatment discontinuations the random effects model produced the better fit.

Overall, consistent/inconsistent model for ARR (fixed effect models (FE)) and treatment discontinuations (random effect (RE) vague models) had similar model fit.

Table 1 Model fit statistics for pooled interferon class-based NMAs (consistent and inconsistent model)

Diagnostic	Consistent model		Inconsistent model	
	Random effects with vague priors	Fixed effects	Random effects with vague priors	Fixed effects
ARR				
Deviance information criterion (DIC)	[redacted]	[redacted]	[redacted]	[redacted]
Total residual deviance	[redacted]	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]	[redacted]
3-month CDA				
Deviance information	[redacted]	[redacted]	[redacted]	[redacted]

criterion (DIC)				
Total residual deviance				
SD				
6-month CDA				
Deviance information criterion (DIC)				
Total residual deviance				
SD				
Treatment discontinuations				
Deviance information criterion (DIC)				
Total residual deviance				
SD				

Note: the model with better fit was determined based on a lower deviance information criterion (**bolded)**.
*Analysis of inconsistency was not conducted. Inconsistency analyses were conducted for the base case analysis only (fixed effects for ARR and CDA outcomes; random effects for the treatment discontinuations outcome).

Comment 1.2 Analysis of inconsistency in the pooled interferon class-based analyses: overall, ARR, 3-month and 6-month CDA and treatment discontinuations demonstrated good consistency (ACD 3.10 – page 11)

In addition to the request for model fit statistics, the Committee noted that it would also be useful to see an inconsistency assessment for the NMA of pooled interferons. An important assumption underlying the NMA is that the analysed network is consistent, meaning that there is no evidence of disagreement between the direct and indirect evidence being combined. (Dias, et al., 2011) For example, whether the direct evidence of ponesimod vs placebo through the phase 2 ponesimod trial is in alignment with indirect evidence e.g., via OPTIMUM (ponesimod v teriflunomide) and then TEMSO (O'Connor, et al., 2011)/TOWER (Confavreux, et al., 2014) (teriflunomide v placebo). An unrelated mean effects model (i.e., an inconsistency model) based on the NICE technical support document (TSD) 4 was used to assess potential inconsistency. (Dias, et al., 2011) To identify any loops where inconsistency was present, the posterior mean deviance of: i) individual data points for ARR and all-cause treatment discontinuations, and ii) individual studies for 3-month and 6-month CDA, in the inconsistency models was plotted against the posterior mean deviance in the consistency models.

Below we present the results for the posterior mean deviance for ARR, 3-month CDA, 6-month CDA and treatment discontinuations. On the plots, consistency is assessed by considering how close all points are to the line X=Y (consistent NMA = inconsistent NMA).

The inconsistency results for ARR, 3-month CDA, 6-month CDA and treatment discontinuations signify that the outcomes generally demonstrated good consistency. For 3-month and 6-month CDA, the DIC

was significantly lower in the inconsistent model (a difference of 5 or more is considered significant, based on NICE TSD 3 (Dias, et al., 2011)). However, the deviance information criterion and total residual deviance and the posterior deviance (Figures 1-4) were similar between the consistent/inconsistent model (FE model). Therefore, it can be concluded that the consistency assumption was not violated.

Outliers are any points where posterior deviance (for either the consistent or inconsistent model) is substantially high. Alternatively, a potential inconsistency is signalled in cases where the posterior deviance is very different between the inconsistent and consistent models (points fall outside of the line X=Y). Some outliers exist, but these are not unexpected given the heterogeneity that we know is present in multiple sclerosis (MS) trials owing to the age of some trials, the difference in outcome definitions and the results from some trials not always aligning with expert clinical knowledge of the products. Outlier effects in these plots may also arise due to random chance in these analyses.

The red points in the figures below highlight potential inconsistencies and outliers in the results i.e., these are not necessarily inconsistencies in the results, but may be potential sources. Similarly, outlier points do not necessarily indicate an inconsistency, but they point to potential outliers. Furthermore, some of the outlier studies had similar results for consistent and inconsistent analyses i.e., they fell on the line – this indicates there was no impact on fit.

Overall, we note that the pooled NMA results are generally representative of the results that would be expected in clinical practice, this was also noted by the clinical experts at appraisal committee meeting (ACM) 1, who commented that "*the results of the network meta-analyses generally reflected which treatments are considered more effective in the NHS*".

Please note for figures 1- 4 the X and Y axis are not on a comparable scale.

Figure 1 Posterior Mean Deviance for ARR, Consistent versus Inconsistent model (Fixed Effects)

Note: threshold for colouring points in red as outliers (high deviance) was set at 2.5.

For the ARR outcome, overall, the results satisfy the consistency assumption and there was generally no disagreement between the models. However, the CombiRx (Lubin, et al., 2013) trial was an outlier: it should be noted that the reported ARR for both arms of the trial were lower than the ARR reported for the same treatments in other trials. Authors of the primary publication for CombiRx (Lubin, et al., 2013) acknowledged this finding: "*The protocol defined ARRs are among the lowest reported to date for the agents utilized in this study, or any other pivotal study with other MS therapeutic agents that utilized similar definitions.*" Authors suggested that a more rigid definition of relapses in CombiRx (Lubin, et al., 2013) was a potential reason for these

findings. Additionally, in the analyses of ARR, the alemtuzumab 12mg (once daily) arm of CAMMS223 (Panitch, et al., 2008) was highlighted due to high posterior deviance. But in this particular case, falling on the line indicates there is not a consistency issue. Therefore, this is not a violation of the consistent assumption of the NMA as the deviance was high in both models. Moreover, the treatment effect estimates were similar between the consistent and inconsistent model, suggesting no disagreements between the two models (thus, not a concern from a consistency standpoint). Therefore, as an overall conclusion ARR results from the pooled interferon class-based model are appropriate.

Figure 2 Posterior Mean Deviance for 3-month CDA, Consistent versus Inconsistent model (Fixed Effects)

Note: threshold for colouring points in red as outliers (high deviance) was set at 2.5.

For the analysis of 3-month CDA, there were no trials that were highlighted as potential inconsistencies in the data despite there being some trials appearing far from the line it is important to note that the Y axis is numerically not as high as the Y-axis for ARR. Overall, it can be concluded that the consistency assumption was not violated as the posterior deviance from the consistent/inconsistent models were relatively similar i.e., the points fell close to the line Y = X.

Figure 3 Posterior Mean Deviance for 6-month CDA, Consistent versus Inconsistent model (Fixed Effects)

Note: threshold for colouring points in red as outliers (high deviance) was set at 2.5.
Similar to the analysis of ARR, for the 6-month CDA (Figure 3), CAMMS223 (Panitch, et al., 2008) was also highlighted because it had high posterior deviance (it should be approximately 1 but it was about 3.6 in both models). This suggests that both models did not fit the study well. However, this is not a violation of the consistent assumption of the NMA as the deviance was high in both models. The treatment effect estimates were similar between the consistent and inconsistent model, also suggesting no disagreements between the two models (thus, not a concern from a consistency standpoint). Therefore overall, it can be concluded that the consistency assumption was not violated as the posterior deviance from the consistent/inconsistent models were relatively similar i.e., the points fell close to the line Y = X.

Figure 4 Posterior Mean Deviance for Treatment discontinuations, Consistent versus Inconsistent model (Random Effects with Vague Priors)

Note: threshold for colouring points in red as outliers (high deviance) was set at 2.5.

In the analysis of treatment discontinuation, the phase 2 study of ocrelizumab was highlighted as a potential source of inconsistency. Again, it is noted that the treatment effect estimates were similar between the consistent and inconsistent model suggesting no disagreements between the two models (thus, not a concern from a consistency perspective.

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Section 1b: An updated NMA based on a hierarchical class demonstrated consistency of results with the original pooled NMA (comments 1.3 – 1.5)

In section 3.10 of the ACD the Committee noted that it may generally be appropriate to consider the results from the interferon studies in a class-based analysis since clinically, evidence and expert opinion indicate that the interferons have comparable efficacy. In section 3.10 of the ACD the Committee also noted that they would prefer to see a hierarchical class-based model as it may be more appropriate than assuming a single, pooled treatment effect.

Comment 1.3. The hierarchical class-based model may be an appropriate analysis for decision making, but the ADVANCE and INCOMIN trials are outliers and should be excluded based on their clinically implausible results as clinical expert feedback from the ofatumumab and ocrelizumab appraisals. (ACD 3.10 – page 11)

To fulfil the Committee's, request a class effect hierarchical NMA model based on Dias, et al., 2018 was applied to data of the main analysis submitted previously. The class effect hierarchical NMA model is an extension of the standard NMA models from NICE TSD 2 (Dias, et al., 2011) where therapies with similar mechanisms of action fall into the same class and their treatment effects are modelled as exchangeable. The hierarchical model assumes the relative effects of treatments within a class come from a common class distribution (i.e., the relative effects are exchangeable). Exchangeability is a key assumption of hierarchical models and assumes that all treatment effects within a class are similar. This assumption allows the model to borrow data (or strength) from treatments within the same class. Furthermore, it is possible to include studies that compare treatments within the same class in the class effect hierarchical NMA model. These studies are useful for informing the within-class variability. It should be noted that this method uses random effects to model class effects which introduces additional variability in the treatment effect resulting in wider credible intervals. However, we have accounted for the credible intervals in the iterations run in the probabilistic model results i.e., we ran 10,000 iterations of the results (see comment 4.2 - 4.3).

The hierarchical class-based model can include all interferon trials reporting eligible outcome data, including trials which compared interferons to interferons, which was not possible in the pooled interferon NMA analysis submitted previously. However, since all studies of interferons contribute to the interferon class estimates, it was considered important to carefully consider potential violations of the exchangeability assumption for these analyses, and as such it was decided that the ADVANCE and INCOMIN trials be excluded. The exclusion of both ADVANCE and INCOMIN are consistent with the most recent appraisal of ofatumumab (TA699) and were also discussed in the appraisal of ocrelizumab (TA533). There are also sources of data, including publications and clinical expert opinion, that note the unexpectedly high efficacy in the two trials and therefore deems them to be outliers. We discuss some of the issues with these trials below:

- ADVANCE trial (peginterferon)

The ADVANCE trial was a phase 3, double-blind, multi-centre, placebo controlled randomised controlled trial, which lasted 48 weeks. After the initial 48-week period of the trial, patients in the placebo group were re-randomised in a 1:1:1 ratio to receive either an injection of peginterferon beta-1a 125 mcg every 2 weeks or every 4 weeks, or alternatively to receive placebo, for a double-blind controlled period of 48

weeks. It is important to note that only the 2-week dosage frequency is licensed and used in clinical practice. (NICE, 2020)

In recent appraisals the ADVANCE trial was excluded from the NMAs of ofatumumab (TA699) (NICE, 2021) and ocrelizumab (TA533) (NICE, 2018) with ERG and Committee agreement, because peginterferon was shown to be more effective than other beta-interferons and high-efficacy treatments such as natalizumab, (which is contrary to clinical experience and is clinically implausible). In the appraisal of ocrelizumab (TA533) (NICE, 2018) the NICE Committee found clinically implausible results were caused by inclusion of the ADVANCE trial in an NMA of time to 6-month confirmed disability progression (CDP-6). In the appraisal of ofatumumab (TA699) (NICE, 2021), the Committee agreed the trial was an outlier. It was originally discussed by the clinical experts in the appraisal of ocrelizumab (TA533) (NICE, 2018) (and revisited during the appraisal for ofatumumab [TA699]) that the fact that results from ADVANCE showed peginterferon as having greater efficacy as natalizumab lacks clinical face validity. In addition, in the multiple technology appraisal (MTA) of beta interferons and glatiramer acetate (TA527) (NICE, 2018) the Assessment Group report noted "(peginterferon), *in particular, relied on one trial with one year of follow-up connected to evidence networks only via placebo.*" Given that class estimates for interferon would be particularly impacted by violations of the assumption of exchangeability, it was deemed unsuitable to include such a flawed trial, which has been cautiously examined in several previous appraisals to be inappropriate, and as such the class estimates could be greatly impacted by an outlier trial. (NICE, 2021).

- <u>INCOMIN (interferon beta 1b)</u>

The INCOMIN trial was a 2-year, prospective, randomised, multicentre trial, comparing interferon beta-1b every other day to interferon beta-1a weekly. The INCOMIN trial was randomised, but it was an open-label trial. INCOMIN only included 188 participants.

Discussed originally in the appraisal of ocrelizumab (TA533) and also in the appraisal of ofatumumab (TA699), the results of INCOMIN were noted to be inconsistent with results from phase 3 trials of interferon 1b and 1a in that, INCOMIN found patients receiving interferon beta-1b every other day had improved outcomes compared to patients receiving a weekly dose of interferon beta-1a. During the appraisal of ofatumumab (NICE, 2021), the company noted that INCOMIN was an "*outlier and not reflective of clinical practice*" in which the ERG agreed. Additionally, several other studies indicated no clinically significant differences between the two treatments (Vartanian, 2003), which is generally in line with clinical opinion.

In both the appraisal of ocrelizumab (TA533) and ofatumumab (TA699), the Committee agreed that the results produced by the INCOMIN study were clinically implausible, and therefore that it was an outlier trial. Again, for the reasons stated above, it was considered inappropriate to include the INCOMIN study in the hierarchical NMA. We would also like to note that it is not possible to include results for INCOMIN in either the 3-month or 6-month disability network due to 3-month disability not being reported and 6-month not being reported in the form of a hazard ratio. Therefore, it would only be possible to report INCOMIN for ARR and treatment discontinuation. (NICE, 2021).

Comment 1.4 Overall, the results of the hierarchical class-based interferon NMA are broadly aligned to the pooled interferon class-based NMA

The requested class-based hierarchical model uses random effects to model the class-based effects. The class effect hierarchical model is used when there are treatments in the network with similar mechanisms of action, and where it is reasonable to assume that there is alignment in the action of treatments from the same class. This contrasts with the standard NMA model from NICE TSD2 (Dias, et al., 2011) where treatments in a network are assumed to be independent of each other.

Overall, the fit of this model is similar to the previous NMAs based on total residual deviance. Due to the hierarchical model utilising random effects to model class effects, the wider credible intervals observed with the hierarchical model are expected, however we do note that between-trial heterogeneity is an issue across the network. This could be a rationale for not using the more complex hierarchical approach and instead using results from the original pooled interferon class-based NMA, and at the least for considering the pooled interferon NMA as potentially more appropriate.

- Annualised Relapse Rate (ARR)

In general, the median estimates of the class-level treatment effects from the hierarchical class-based model are aligned with previously conducted analyses where interferon regimens were pooled. The effect estimates from the hierarchical class-based model have wider credible intervals.

Despite the wide credible intervals, the results for ARR are broadly consistent with the results seen in the previous pooled interferon class based NMAs, with the most effective treatments being the monoclonal antibody treatment ofatumumab, natalizumab, ocrelizumab and alemtuzumab.

Figure 5 Forest Plot (Ponesimod versus Treatments) for ARR (excluding ADVANCE and INCOMIN): Interferon Class Treatment Effect; Fixed Effects Model for Individual Effects

- 3-month CDA

In general, the median estimates of the class-level treatment effects from the hierarchical class-based model are aligned with previously conducted analyses where interferon regimens were pooled. Again, the effect estimates from the hierarchical class-based model have wider credible intervals.

For 3-month CDA, again we note the trend that ofatumumab, ocrelizumab and alemtuzumab are indicated as being more effective than ponesimod, with the remaining treatments being similar or less effective than ponesimod.

Figure 6 Forest Plot (Ponesimod versus Treatments) for 3-month CDA [excluding ADVANCE]: Interferon Class Treatment Effect; Fixed Effects Model

- 6-month CDA

Overall, the 6-month CDA median estimates from the hierarchical class-based model are aligned with previously conducted analyses where interferon regimens were pooled and again demonstrate wider confidence intervals.

For 6-month CDA, ofatumumab, ocrelizumab, alemtuzumab and natalizumab are indicated as being more effective than ponesimod, with the remaining treatments being equal or less effective than ponesimod.

Figure 7 Forest Plot (Ponesimod versus Treatments) for 6-month CDA [excluding ADVANCE trial]: Interferon Class Treatment Effect; Fixed Effects Model

- Treatment discontinuations

Similar to efficacy outcomes, the median estimates of the class-level treatment effects for treatment discontinuations are aligned with previously conducted analyses where interferon regimens were pooled. The effect estimates also have wider credible intervals, but again this is due to the nature of the model and is to be expected.

Figure 8 Forest Plot (Ponesimod versus Treatments) for Treatment Discontinuations [excluding ADVANCE & INCOMIN trials]: Interferon Class Treatment Effect; Random Effects with Vague Priors

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Comment 1.5 Model fit statistics for hierarchical class-based model: the hierarchical class-based NMA model generally fit the data well

For transparency, we have provided the Committee with model fit statistics for the hierarchical class-based NMA. Generally, no clear gains/losses were found in terms of model fit (based on total residual deviance).

The hierarchical class-based model fit the data relatively well, based on the total residual deviance being close to the number of data points, for each outcome. Overall, there were uncertainties with the class effect as the 95% credible intervals of the standard deviations (SDs) was wide for all outcomes, but with this type of model this is to be expected. Overall, the hierarchical class-based NMA model is appropriate for decision making, furthermore the overall conclusions based on the point estimates of the hierarchical NMA are broadly in line with the conclusions of the previously conducted pooled interferon class NMA.

Table 2 Model fit statistics for hierarchical class-based model analyses

Diagnostic	ARR (fixed effects)	3-month CDA (fixed effects)	6-month CDA (fixed effects)	Treatment discontinuations (random effects with vague priors)
Deviance information criterion (DIC)	[redacted]	[redacted]	[redacted]	[redacted]
Total residual deviance	[redacted]	[redacted]	[redacted]	[redacted]
Beta	[redacted]	[redacted]	[redacted]	[redacted]
SD for individual level effects	[redacted]	[redacted]	[redacted]	[redacted]
SD for class level effects	[redacted]	[redacted]	[redacted]	[redacted]

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Section 2: Revision of mortality data in the model sourced from Harding, et al., 2018, where previously Pokorski, 1997 was the main source, better reflects current clinical practice, due to mortality values from the new study representing mortality of patients seen in current UK clinical practice (comment 2.1)

For the majority of appraisals in MS, Pokorski, 1997 has been used as a source of mortality in each company economic model. This has been accepted numerous times by the Committee in the past for the appraisals of ofatumumab (NICE, 2021), peginterferon (NICE, 2020), ocrelizumab (NICE, 2018), daclizumab (NICE, 2017), dimethyl fumarate (NICE, 2014), alemtuzumab (NICE, 2014), teriflunomide (NICE, 2014), fingolimod (NICE, 2012), and natalizumab (NICE, 2007). However, the clinical experts considered that this mortality data was now outdated and not reflective of the natural history based on current clinical practice. They noted that new standardised mortality rates by expanded disability status scale (EDSS) for people with MS had been recently published in the UK. This updated data showed a higher risk of death in higher EDSS states 8 and 9 and so the Committee concluded that an updated analysis with the new mortality data would improve the face validity of the model.

Comment 2.1. Analysis using updated mortality assumptions informed from new evidence: the updated mortality data from Harding et al 2018 improves QALY outputs for patients and aligns economic model outputs closer to outputs the Committee would expect (ACD 3.10 – page 11)

In line with this request, we have reviewed the Harding, et al., 2018 paper and subsequently input the mortality states into the economic model. For completeness we were required to make some assumptions: the Harding, et al., 2018 paper only reported mortality ratios for EDSS 4 - 9 and they grouped EDSS 4 and EDSS 5 together. Therefore, we have selected the following rules to complete the EDSS states in the most methodologically appropriate way:

- EDSS 0 - 3 uses the current base case value derived from the Pokorski 1997
- EDSS 4 - 5 use the same value from Harding 2018
- EDSS 6 - 9 use individual values from Harding 2018.

The main difference between Pokorski, 1997 and Harding, et al., 2018 is on the higher EDSS mortality risk i.e., EDSS 8 and 9, this is where the Committee were most interested in observing changes in the updated mortality data and where the greatest change can be seen in the scores. Due to missing EDSS states and the lower impact of disease in 0-3, it is more appropriate to utilise the Pokorski, 1997 data to complete the EDSS scale. A source of data was required to fill the gap in the missing data from Harding, et al., 2018. Therefore, given that mortality is not a key driver in EDSS 0 - 3 we utilised the Pokorski data to fill the gap, but don't anticipate much impact from this, and believe that the Pokorski data is the most appropriate source.

To test the impact of changes that the mortality data update had on the model, we captured the quality adjusted life year (QALY) outputs using the pooled NMA model and with the Pokorski et al 1997 data and then also with the new Harding, et al., 2018 data. The results are detailed in table 3 below.

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Table 3 Mortality outputs based on a comparison of Pokorski vs Harding et al

	Ponesimod	Teriflunomide	Dimethyl Fumarate	Glatiramer Acetate	Interferon Class	Ocrelizumab	Ofatumumab
Pokorski et al 1997 data							
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Caregivers	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Harding et al 2018 data							
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Caregivers	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Overall, there was an increase in QALYs with the new mortality data, by approximately 1 QALY, although there was slightly more of a QALY increase for glatiramer acetate and ofatumumab than for the other comparator treatments. The new mortality data did not significantly change the estimates of cost-effectiveness. But as expected, total life years decreased (by ~4 years) with the new mortality data. The total QALYs increased, however, due to more patients dying from the high EDSS states (NB – patients in EDSS 8 and 9 have negative utility values so they are worse off than the dead patients for the purpose of the economic model).

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Section 3: The QALY outputs produced by the ponesimod model for patients and the rate of time spent in RRMS and SPMS states is consistent with previous other models accepted by NICE in multiple sclerosis (comments 3.1 – 3.2)

In section 3.13 of the ACD, the Committee noted that "*the modelled outputs, including total quality adjusted life year (QALY) gain, from the economic model were inconsistent with other appraisals*". In addition, the Committee also queried "*why the company analysis modelled that people would spend a greater amount of time in the secondary progressive multiple sclerosis state*". Below we have investigated the outputs in more detail and discussed the outputs of the ponesimod economic model in relation to the proportion of patients who spend time in the relapsing remitting multiple sclerosis (RRMS) and secondary progressive multiple sclerosis (SPMS) states in past appraisals.

Comment 3.1 Overall the ponesimod model's QALYs are consistent with those in recent appraisals of ofatumumab (TA699) and peginterferon (TA624). The outputs for beta interferons and glatiramer acetate (TA527) are unusually high, but it is not possible to determine why this is, due to a lack of details around the inputs used in TA527.

To understand further if the modelled outputs for ponesimod were aligned to previous appraisals it was possible to review recent NICE comparator MS appraisals input data. However, it is important to note that several of the outputs from published appraisals are heavily redacted, so we believe the most appropriate method of exploration and alignment is via an assessment of the available QALYs from unredacted appraisals.

We reviewed the more recent NICE appraisals in MS, (since older appraisals may not align on outputs appropriately) including the appraisals of ofatumumab (TA699) (NICE, 2021), peginterferon (TA624) (NICE, 2020) and the multiple technology appraisal (MTA) of beta interferons and glatiramer acetate (TA527) (NICE, 2018). Unfortunately, it was not possible to review the QALY outputs from ozanimod (TA706) (NICE, 2021) and ocrelizumab (TA533) (NICE, 2018), since all QALY information was redacted.

Reviewing the three past appraisals provides a general understanding of the total QALYs gained from each treatment in its respective economic model. The outputs in ofatumumab (TA699) (NICE, 2021) and peginterferon (TA624) (NICE, 2020) ranged from approximately 3.5 QALYs up to approximately 6 QALYs for higher efficacy treatments, and for treatments given to patients with highly active disease. It is important to note that there were variations in QALY outputs based on different input sources, the treatment population, and scenario analyses. However, generally the QALYs fell within the 3.5 to 6 range, except for the QALY outputs for the MTA appraisal of beta interferons and glatiramer acetate (TA527) (NICE, 2018). On average, the MTA QALYs were much higher than the other appraisals with QALY ranging from ~ 8 to ~10 QALYs, again depending on scenario and inputs.

For a more direct comparison against the ponesimod model, we reviewed the three appraisals in further detail; ofatumumab (TA699) (NICE, 2021), peginterferon (TA624) (NICE, 2020) and the MTA (TA527) (NICE, 2018) with the aim of aligning model inputs to the ponesimod model to understand if the modelled outputs of ponesimod directly produced similar QALYs to those stated in the comparator's original submissions. To undertake this scenario analysis, we attempted to select the appraisal/s where most inputs were visible so that we could replicate these in the ponesimod model:

- Comparison vs. TA699 (ofatumumab): we were able to align on some inputs, but not all required inputs due to a lack of detail provided and some redactions in the company submission, for example details of the NMAs. The difference in QALYs for common comparators for the ofatumumab base-case and ponesimod base-case presented at ACM 1 indicate that the QALY outputs are generally comparable to between the two models. However, it was not possible to take the analysis further to fully align on the model inputs, and we therefore could not use ofatumumab for the benchmarking exercise.

- Comparison vs. TA527 (NICE MTA): Some of the key assumptions in the MTA model are excluding carer disutility and no MS-related excess mortalities. After aligning on those inputs, there is still a significant difference in the QALY output (5.1 ponesimod base-case vs. 9.6 in the MTA base-case from the Assessment Groups pooled base-case). It is possible the two models in the MTA used different natural disease progression transition probabilities (from RRMS to SMPS), but no details were provided. It was also very difficult to understand which were the key base-case assumptions for the model and what values were used. Due to this it was not possible to fully align on model inputs. The large QALY values from this appraisal are not consistent with the ponesimod model or the more recent appraisals in MS. Unfortunately, without access to the model and full model inputs it was not possible to explore why this is.

- Comparison vs. TA624 (Peginterferon): the peginterferon model structure is very similar to the ponesimod model, additionally we were able to align on almost all the model inputs as these were detailed in the submission clearly, except for the treatment effects which were based on the company NMAs, which are redacted, and the life tables (very minimal impact). Despite this, there is enough available information to undertake scenario analysis with this appraisal. We explored scenarios using our original inputs based on hazard ratios as transition probabilities i.e., before they were converted to risk ratios by the ERG/Committee since this was in the pooled interferon ponesimod model and has been used in previous appraisals. To conduct the testing, we took the known inputs from the peginterferon appraisal and used them in the ponesimod model to try to replicate results detailed in the original peginterferon submission.

Table 4 outlines each of the inputs used in the peginterferon model and where the original model does or does not align with the inputs in the ponesimod model. From the table there are 4 inputs that did not align between the two models, these are baseline characteristics, which come from each company's respective trials, transition from RRMS to SPMS, treatment discontinuations and carer disutility. It is not possible to fully align to NMA outputs as these are confidential and are therefore redacted.

Table 4 Ponesimod model comparison to peginterferon (TA624)

Input	Peginterferon model source	Alignment with ponesimod model
Baseline characteristics	ADVANCE trial	Re-aligned to TA624*
Natural history RRMS	British Columbia	Original ponesimod model aligned with TA624
Transition from RRMS to SPMS	London Ontario	Re-aligned to TA624*
Natural history SPMS	London Ontario	Original ponesimod model aligned with TA624

Natural history relapse	UK MS survey/Patzold 1982	Original ponesimod model aligned with TA624
Treatment effect	6-month disability/relapse	Original ponesimod model aligned with TA624
Treatment discontinuation	All-cause from trial	Re-aligned to TA624*
Stopping rule	EDSS>=7/progression to SPMS	Original ponesimod model aligned with TA624
Waning	25% after 2 years/50% after 5 years	Original ponesimod model aligned with TA624
Utility	Orme et al 2007	Original ponesimod model aligned with TA624
Carer disutility	Acaster 2013	Acaster 2013 directly re-aligned to TA624*
Mortality	General population mortality (2016) and Pokorski et al 1997 (no interpolation)	General population mortality (2020) and Pokorski et al 1997 (interpolation)*
Other notable inputs	NMA for disability and relapses redacted	NMA for disability and relapses from Janssen NMA*

*Deviates from Janssen base case analysis

The results of the scenario analysis comparison are detailed in table 5. The scenario analysis for the two sets of inputs, results in QALYs for comparators common to both appraisals ranging from [redacted] and [redacted]. This indicates that the QALY outputs are very comparable between the two sets of results for the ponesimod and peginterferon models. Overall, the QALY outputs from the pooled interferon ponesimod model were between just below 3 QALYs to just below 5 QALYs on average. This generally aligns to the outputs of the ofatumumab and peginterferon appraisal outputs of 3 QALYs up to ~6 QALYs and the number of QALYs was very comparable.

Table 5 Results of alignment between ponesimod and peginterferon (TA624)

Treatment	QALYs (Janssen model)	QALYs (peginterferon model inputs)	Difference
Teriflunomide	[redacted]	[redacted]	[redacted]
DMF	[redacted]	[redacted]	[redacted]
GA 20	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]

We note that while it was possible to isolate some of the key model inputs, it was not possible to assess the impact of the comparator company's NMA results, which we believe are likely to be a key driver in the small difference between the QALY outputs, alongside baseline characteristics. It is worth also noting that the company NMA results will have likely changed over time as more treatments become available. However, from the scenario analysis the inputs which resulted in the most notable changes in QALY values include:

- the Committee/ERG conversion of hazard ratios to risk ratios; this change did not have a significant impact on the QALY values but did reduce them on average by 1% - 3% depending on the comparator. This was not included in this scenario, but when reviewing the old model (pre-ACM 1 to post ACM 1) a small change in the QALYs was noted.

- Removal of caregiver disutility, as was done in TA527 (potentially one contribution to the higher QALY values in the MTA)
- Baseline characteristics – based on trial data.

In conclusion, the outputs for the ponesimod model are comparable to the outputs from the most recent appraisals of peginterferon (TA624) (NICE, 2020) and ofatumumab (TA699) (NICE, 2021). There are differences in inputs based on trial data and the resulting NMA inputs, which are likely to have a significant impact on the results. Despite this, the overall range of QALYs between ponesimod and the two appraisals are broadly aligned. We also note that the QALY outputs from the MTA of beta interferons and glatiramer acetate (TA527) (NICE, 2018) are unusually high, but we cannot isolate the inputs due to a lack of clarity in the appraisal. Overall, we believe that the economic model based on the pooled interferon NMA is robust, consistent with previous appraisals and appropriate for decision making based on this comparison exercise with the most recent appraisals.

Comment 3.2 Modelled outputs for time spent in SPMS from the ponesimod model are consistent with previous appraisals, notably peginterferon (TA624)

To explore the Committee's request to investigate the time spent in the SPMS state by patients in the ponesimod model, we have reviewed previous appraisals to understand which state patients spend most time in from other appraisals, and where possible we have conducted scenario analysis around the assumptions.

After further exploration of the economic model and outputs (as discussed in comment 2.1) we observed that the ponesimod model's QALY estimates are related to the time spent in RRMS and SPMS states, since patients with SPMS (a) have lower utility and (b) are also more likely to progress to later disease stages, therefore they have lower utility values.

To further understand the SPMS outputs the ponesimod model is producing, we conducted two activities:

- a review of time spent in SPMS reported from the peginterferon appraisal for established comparators (due to the availability of unredacted inputs)
- a scenario analysis putting peginterferon inputs into the ponesimod model to test outputs.

We calculated the time spent in SPMS in the peginterferon model using the undiscounted life years reported in the TA624 appendix, Table 102. For example, the time spent in SPMS for teriflunomide is 65.5%, calculated as (34.46 total life years - 11.89 years spent SPMS free) / (34.46 total life years).

Results from the Janssen model with ponesimod inputs compared to results produced replacing ponesimod model inputs with those from peginterferon are presented in table 6. For comparison, the table also includes the results of time spent in SPMS reported directly from the peginterferon appraisal.

When comparing the time spent in SPMS directly from the peginterferon appraisal, it was observed that on average 65% of the time was spent in the SPMS disease state based on the peginterferon model, with patients spending the most time in SPMS when receiving glatiramer acetate and the least time in SPMS when receiving ocrelizumab, with teriflunomide and dimethyl fumarate being second and third, respectively. These results are consistent with the SPMS outputs directly from the ponesimod model, where patients spent on average [redacted] of their time in SPMS, and the same order of time spent in SPMS

based on treatment type i.e., spending the most time in SPMS when receiving glatiramer acetate, then dimethyl fumarate, then teriflunomide and the least when receiving ocrelizumab out of the four treatments.

Table 6 Time spent in SPMS stated in ponesimod and peginterferon model

Treatment	% Time spent in SPMS (Janssen base case analysis a)	% Time spent in SPMS (Janssen model with Peg inputs b)	% Time spent in SPMS (peginterferon model c)	Difference (column b – column c)
Teriflunomide	[redacted]	[redacted]	[redacted]	[redacted]
Dimethyl Fumarate	[redacted]	[redacted]	[redacted]	[redacted]
Glatiramer Acetate	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]

We conducted additional scenario analysis, which replaced the peginterferon input data with the data in the ponesimod model in order to test whether the ponesimod model could replicate the time spent in SPMS stated in the peginterferon submission. We were able to retrieve most inputs from the peginterferon submission except for the company's own NMA analysis. Due to this, some variation was expected, but we saw that the ordering of highest to lowest time spent in SPMS did not change i.e., teriflunomide, dimethyl fumarate, glatiramer acetate and ocrelizumab. In addition, the results were relatively consistent with the outputs noted in the peginterferon model itself. Therefore, it could be concluded that the ponesimod model is highly aligned to the peginterferon model results for time spent in SPMS.

Please note that the scenario analysis was based on the pooled interferon class-based NMA model and not on updates using the hierarchical class-based NMA results. We note, that since the Committee/ERG updated the hazard ratios (HR) to relative risks (RR) this is part of the model engine and results have been calculated on risk ratios and not hazards, due to this version being presented at ACM 1. Although the change from HR to RR does not have a significant impact to the model outputs, there is a small difference in QALYs, where QALYs are greater with HR over RR, so the change implemented by the ERG/Committee has reduced the QALY's slightly.

Overall, the outputs for time spent in SPMS are broadly consistent between ponesimod and peginterferon, we have validated the ponesimod model structure and ensured that there are no errors in the model causing unreliable or unpredictable outputs. In addition, the models QALY estimates are related to time spent in SPMS states, since patients with SPMS will clinically have a lower utility and will therefore likely progress to later disease stages, which in turn also has lower utility values associated.

As requested by the Committee, several changes have been made to the model to produce a new base case model. The updated changes and their impact on the model outputs and time spent in SPMS are discussed in comment 4.1 – 4.4 However, we would like to note here, that the inclusion of mortality from the Harding et al 2018 source as opposed to Pokorski, 1997 source, results in increased QALY outputs and hence a more even split of patient time spent in RRMS and SPMS states.

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Section 4: The hierarchical class-based model and updated mortality data produce outputs in the cost effectiveness model in line with changes in MS treatment that the Committee expected to see in ACM 1. The updated economic model is likely to better reflect current clinical practice, due to mortality values from the new study representing mortality of patients seen in current UK clinical practice and overall, the model demonstrates that ponesimod is a cost-effective option for MS. (comments 4.1 – 4.5)

In the ACD, the Committee requested to see revisions to some core data inputs in the economic model, and so we have revised the base case model in line with the Committee's request. Below the new model inputs and resulting impact on the model conclusions are discussed. Please note the cost effectiveness results have been produced based on the revised ponesimod PAS compared to the published list price of the comparator treatments.

Comment 4.1. Results of new base case economic model: the overall cost-effectiveness of the economic model remains the same in the revised economic model i.e., ponesimod is a cost-effective treatment option for patients with active and highly active RRMS
(ACD 3.10 – page 11)

The new base-case model assumes the following key inputs:

Input	Pooled NMA economic model inputs (presented at ACM 1)	Revised model updated during ACD
NMA	Based on the pooled class-based interferon NMA	Hierarchical class-based interferon NMA
Mortality	Pokorski, 1997	Harding et al 2018 (with Pokorski, 1997 data for EDSS states 0 – 3)
Annual conversion probability from RRMS to SPMS	Mauskopf, et al., 2016	ERG revision of Mauskopf, et al., 2016 from peginterferon submission
Transition probability matrices	Janssen model HR in line with previous models in MS. ERG made a switch upon Committee lead team request prior to committee meeting to convert HRs to RRs	Revised model keeps the RR switch

Overall, with the revised model inputs there is minimal change in cost-effectiveness estimates in the hierarchical class-based NMA relative to the pooled interferon class NMA. This denotes that the two NMAs are aligned.

Results of the economic model with the hierarchical class-based NMA result in the following: in active RRMS, ponesimod is cost effective and is dominating (i.e., higher clinical outcomes and cost saving) teriflunomide, dimethyl fumarate, glatiramer acetate, the interferon class (and ozanimod) which are all first line treatments in RRMS. Ocrelizumab and ofatumumab were more costly and more effective than ponesimod as monoclonal antibody treatments. However, this could still be seen as a cost-effective use of resources. It is also important to note that neither ocrelizumab or ofatumumab are orally administered, requiring administration either by intravenous infusion or via subcutaneous injection, respectively, and so patients who are considering them as treatment options, will likely not be the same patients who are

considering an oral DMT such as ponesimod. Furthermore, oral treatments are generally preferred by patients.

It is important to note that the cost-effectiveness of the deterministic and probabilistic results for the active RRMS population align to the cost-effectiveness results presented in the economic model using the pooled interferon NMA. In highly active RRMS, again the conclusions that can be inferred are the same between the pooled NMA and Pokorski, 1997 mortality data and the hierarchical NMA and Harding, et al., 2018 source of data. Ponesimod dominates fingolimod, is less effective and less costly than ocrelizumab and alemtuzumab and is dominated by cladribine. It is important to note however that the Committee recognised that cladribine has a substantially higher treatment effect, in particular for 6-month disability progression, which is not supported by clinical practice, as noted by the clinical experts during the committee meeting.

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Comment 4.2 Deterministic and probabilistic results for the ITT RRMS population

The probabilistic results have been run based on 10,000 iterations of the economic model. We note that the probabilistic results are consistent with the deterministic results and indicate that ponesimod is a cost-effective treatment in first line RRMS.

Table 7 CEM base-case results for the ITT population

Cost-Effectiveness Outcomes	Total Costs				Total QALYs				ICER per QALY (Probabilistic)	ICER per QALY (Deterministic)
	Mean (Probabilistic)	95% CI lower	95% CI upper	Deterministic (base case)	Mean (Probabilistic)	95% CI lower	95% CI upper	Deterministic (base case)		
Ponesimod 20mg PO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	–	–
Teriflunomide 14mg PO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominates	Dominates
Dimethyl fumarate 240mg PO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominates	Dominates
Glatiramer acetate 20mg SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominates	Dominates
Interferon class	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominates	Dominates
Ocrelizumab 600mg IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Less Effective and Less Costly	Less Effective and Less Costly
Ofatumumab 20mg SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Less Effective and Less Costly	Less Effective and Less Costly
Ozanimod 1.0mg PO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominates	Dominates

Figure 9 Cost-effectiveness scatter plot for ITT population

Figure 10 Cost effectiveness acceptability curve for the ITT population

Comment 4.3: Deterministic and probabilistic results for the highly active RRMS population

The probabilistic results have been run based on 10,000 iterations of the economic model. We note that the probabilistic results are consistent with the deterministic results and indicate that ponesimod is a cost-effective treatment in highly active RRMS.

Table 8 CEM base-case results for the Highly Active population

Cost-Effectiveness Outcomes	Total Costs				Total QALYs				ICER per QALY (Probabilistic)	ICER per QALY (Deterministic)
	Mean (Probabilistic)	95% CI lower	95% CI upper	Deterministic (base case)	Mean (Probabilistic)	95% CI lower	95% CI upper	Deterministic (base case)		
Ponesimod 20mg PO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	–	–
Ocrelizumab 600mg IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Less Effective and Less Costly	Less Effective and Less Costly
Ofatumumab 20mg SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Less Effective and Less Costly	Less Effective and Less Costly
Ozanimod 1.0mg PO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominates	Dominates
Alemtuzumab 12mg IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Less Effective and Less Costly	Less Effective and Less Costly
Cladribine 3.5mg/kg PO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
Fingolimod 0.5mg PO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominates	Dominates

Figure 11 Cost-effectiveness scatter plot for Highly Active population

Figure 12 Cost effectiveness acceptability curve for the Highly Active population

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Comment 4.4. SPMS and modelled outputs in new model: modelled outputs from the economic model using Harding et al and the hierarchical class-based NMA, produce outputs that the Committee would expect to see in line with current clinical practice (ACD 3.10 – page 11)

As discussed, in the results section (comment 4.1 - 5.3) the updated base case model includes new assumptions based on mortality inputs from Harding et al 2018, switch to peginterferon inputs (NICE, 2020) for annual conversion from RRMS to SPMS (previously updated by the ERG), HR updated to RR (updated by the Committee/ERG prior to ACM 1), and updated inputs via the hierarchical class-based NMA.

In order to review what outputs the revised model produces compared to the model presented at ACM 1 we have undertaken a comparison exercise to review the outputs of the new model in terms of both the modelled QALY outputs and time spent in the SPMS state based on the revised inputs. Below we discuss the changes and results as presented in table 9 and 10:

- The initial model reviewed at ACM 1 included the following inputs: 6-month CDA based on pooled interferon class-based NMA, Mauskopf, et al., 2016 conversion RRMS to SPMS, Pokorski, 1997 with interpolation for mortality and HR to RR as updated efficacy by Committee/ERG.

- For the revised base case the model inputs are as follows: 6-month CDA based on hierarchical interferon class-based NMA excluding ADVANCE/INCOMIN; peginterferon (NICE, 2020) conversion for RRMS to SPMS, Harding et al 2018 for mortality and HR to RR as updated by Committee/ERG.

Table 9 Ponesimod QALY model output based on the model reviewed at ACM 1 and revised base case

Treatment	QALYs (Janssen ACM1 base case)	QALYs (Janssen revised base case)
Ponesimod	[redacted]	[redacted]
Teriflunomide	[redacted]	[redacted]
Dimethyl fumarate	[redacted]	[redacted]
Glatiramer acetate	[redacted]	[redacted]
Interferon class	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]
Ofatumumab	[redacted]	[redacted]

Overall, in the new model there is an increase in QALY outputs by approximately 1 QALY (or slightly more), these results are more closely aligned to the outputs the Committee anticipated to see. However, we note that the changes in inputs does not change the overall cost-effectiveness of the model.

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Table 10 Ponesimod time spent in SPMS in the model reviewed at ACM 1 and revised base case

Treatment	% Time spent in SPMS (Janssen ACM1 base case)	% Time spent in SPMS (Janssen revised base case)	Difference
Ponesimod	[redacted]	[redacted]	[redacted]
Teriflunomide	[redacted]	[redacted]	[redacted]
DMF	[redacted]	[redacted]	[redacted]
GA 20	[redacted]	[redacted]	[redacted]
Interferon class	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]
Ofatumumab	[redacted]	[redacted]	[redacted]

The update of inputs in the economic model has produced a more even split of time patients spend in RRMS and SPMS states. We believe this is likely due to the inclusion of revised mortality data since the mortality data includes a higher risk of death in higher EDSS states particularly states 7, 8, and 9.

As demonstrated, the time spent in SPMS from the ponesimod model presented at ACM 1 is closely aligned to the results displayed in the peginterferon model (NICE, 2020). Pokorski, 1997 inputs have been utilised in the majority of previous appraisals. However, the new mortality data is likely more reflective of clinical practice and patients spending approximately equal time in RRMS and SPMS states.

In conclusion, we consider the model inputs and outputs for the ponesimod model are appropriate and are reflective of the current expectations of MS treatments, in line with comments from the clinical experts.

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Comment 4.5 Scenario analysis of the pooled class-based NMA in the economic model and the hierarchical interferon class-based NMA in the economic model produce similar outputs and do not impact cost effectiveness. There is therefore consistency between the two economic models

In order to examine if the results of the economic model using the pooled interferon class NMA provided similar results to the hierarchical class-based NMA, we conducted a scenario analysis using key model assumptions but maintaining the pooled NMAs to run deterministic results.

Both models used mortality data sourced from Harding, et al., 2018 and employed annual conversion probability of RRMS to SPMS from the peginterferon appraisal, in line with the ERG update. CDA progression was based on 6-month CDA and ponesimod was ran using the revised patient access scheme (PAS) price, while comparator disease modifying treatments (DMTs) were at their respective list prices.

Results for the intention-to-treat (ITT) population are presented in table 11 and results for the highly active population are presented in table 12. Overall, the total costs and QALYs are consistent across both models and are in harmony in terms of the conclusions that can be drawn.

Table 11 Scenario analysis of outputs from economic model using the pooled interferon class-based NMA vs hierarchical class-based interferon NMA for the ITT population

Treatment	Pooled interferon class-based NMA model			Hierarchical interferon-class based NMA		
	Total Cost (discounted)	Total QALY (discounted)	Cost Effectiveness Conclusion	Total Cost (discounted)	Total QALY (discounted)	Cost Effectiveness Conclusion
Ponesimod 20mg PO	[redacted]	[redacted]	—	[redacted]	[redacted]	—
Teriflunomide 14mg PO	[redacted]	[redacted]	Ponesimod Dominates	[redacted]	[redacted]	Ponesimod Dominates
Dimethyl fumarate 240mg PO	[redacted]	[redacted]	Ponesimod Dominates	[redacted]	[redacted]	Ponesimod Dominates
Glatiramer acetate 20mg SC	[redacted]	[redacted]	Ponesimod Dominates	[redacted]	[redacted]	Ponesimod Dominates
Interferon class	[redacted]	[redacted]	Ponesimod Dominates	[redacted]	[redacted]	Ponesimod Dominates
Ocrelizumab 600mg IV	[redacted]	[redacted]	Less costly, Less Effective	[redacted]	[redacted]	Less costly, Less Effective
Ofatumumab 20mg SC	[redacted]	[redacted]	Less costly, Less Effective	[redacted]	[redacted]	Less costly, Less Effective
Ozanimod 1.0mg PO	[redacted]	[redacted]	Ponesimod Dominates	[redacted]	[redacted]	Ponesimod Dominates

Ponesimod for treating relapsing multiple sclerosis [ID1393]

Table 12 Scenario analysis of outputs from economic model using the pooled interferon class-based NMA vs hierarchical class-based interferon NMA for the Highly Active population

Treatment	Pooled interferon class-based NMA model			Hierarchical interferon class-based NMA		
	Total Cost (discounted)	Total QALY (discounted)	Cost Effectiveness Conclusion	Total Cost (discounted)	Total QALY (discounted)	Cost Effectiveness Conclusion
Ponesimod 20mg PO	[redacted]	[redacted]	—	[redacted]	[redacted]	—
Ocrelizumab 600mg IV	[redacted]	[redacted]	Less costly, Less Effective	[redacted]	[redacted]	Less costly, Less Effective
Ofatumumab 20mg SC	[redacted]	[redacted]	Less costly, Less Effective	[redacted]	[redacted]	Less costly, Less Effective
Ozanimod 1.0mg PO	[redacted]	[redacted]	Ponesimod Dominates	[redacted]	[redacted]	Ponesimod Dominates
Alemtuzumab 12mg IV	[redacted]	[redacted]	Less costly, Less Effective	[redacted]	[redacted]	Less costly, Less Effective
Cladribine 3.5mg/kg PO	[redacted]	[redacted]	Dominated	[redacted]	[redacted]	Dominated
Fingolimod 0.5mg PO	[redacted]	[redacted]	Ponesimod Dominates	[redacted]	[redacted]	Ponesimod Dominates

Closing Comments

Janssen have attempted to address all of the Committee's concerns during the allocated consultation period. We conclude that both the pooled interferon class-based NMA and the hierarchical NMA have reasonable fit and that the modelled outputs from both NMAs are consistent with each other. Furthermore, the outputs presented in ACM 1 from the ponesimod economic model are consistent with recent previous appraisals in MS. While updates to the revised base-case economic model (utilising the hierarchical class-based interferon NMA), produce results that do not impact cost-effectiveness and is aligned to the previous pooled NMA reviewed by the Committee.

We note the committee's comments regarding heterogeneity across all trials of MS, but the committee have been able to conclude on approximately 14 treatments in MS with the same evidence base, where the evidence presented for ponesimod is at least as good as (if not improved) and is consistent compared to previous appraisals.

Indeed, the changes to the models do not impact cost-effectiveness results of ponesimod as a treatment option for people with RRMS between the hierarchical class-based NMA and for the pooled interferon class base-case model presented by Janssen at ACM 1. That is, ponesimod is a cost-effective treatment option for patients with active and highly active RRMS. Given the uncertainty raised by issues of heterogeneity in comparator trials, specifically the interferon trials, it is important to note that the data presented for ponesimod is in line with the data presented previously for comparator DMTs and that ponesimod has demonstrated its clinical benefit in a direct head-to-head phase 3 trial vs teriflunomide, while additionally there is up to 10-years of phase 2 data available. Overall, this should provide the Committee with sufficient certainty regarding the treatment effect of ponesimod.

Ponesimod for treating relapsing multiple sclerosis [ID1393]

Section 5: Additional Comments and Factual Inaccuracies in the ACD

Comment 5 Factual inaccuracy (ACD 3.2 – page 5): Ponesimod positioning

In the ACD, NICE noted that "*at technical engagement the company updated its positioning of ponesimod to exclude rapidly evolving severe disease*"; Janssen would like to highlight that ponesimod was always positioned in the active and highly active RRMS treatment lines, since clinical feedback (in line with Committee clinical expert agreement) was that ponesimod would be most beneficial to patients with active and highly active RRMS. This was reflected in our initial submission NMAs and model structure. However, during technical engagement the ERG asked for clarification on positioning since there was a small proportion of patients who could be considered to have Rapidly Evolving Severe (RES) RRMS in the phase 3 OPTIMUM trial in line with NHS England's treatment algorithm.

Comment 6 Misleading statement (ACD 3.4 – page 7): Disability accumulation

In the ACD, NICE highlights that "*OPTIMUM showed a statistically significant difference in annualised relapse rate and change in fatigue-related symptoms for ponesimod compared with teriflunomide. The committee considered the differences seen in 3- and 6-month confirmed disability accumulation were uncertain*". In the phase 3 OPTIMUM trial, the risk for 3-month and 6-month CDA for ponesimod 20 mg compared to teriflunomide 14 mg was estimated to be 17% and 16% lower, respectively, which is consistent between CDA outcomes. Furthermore, the study was not powered to show superiority between the measures (Kappos, et al., 2021). The outcomes of the trial are very much in line with previous trials in MS and we therefore believe this statement to be misleading to the public, as it implies there may be issues with disability outcomes or trial results. If, however NICE are referring to the difference in results seen between the economic model outputs when employing either the 3-month or 6-month CDA, we believe this should have been clearly stated. It is not uncommon to see differences in results from the economic models between 3-month and 6-month disability since the models are driven by NMAs which utilise the entirety of MS data from other company comparator drug trials; as noted in the ponesimod appraisal and during the majority of MS appraisals there is heterogeneity across MS trials in general due to the different populations, outpoints collected, duration of trials conducted, and how recently the trials were conducted. This is not a special situation in the appraisal of ponesimod, since the Committee have seen this issue across all MS appraisals over the years. In recent MS appraisals the themes of heterogeneity between MS trials have always been a discussion point and was discussed to some degree in the appraisals of ofatumumab (TA699) (NICE, 2021), peginterferon (TA624) (NICE, 2020) and ocrelizumab (TA533) (NICE, 2018). However, for each appraisal the Committee were able to make an informed decision and conclude on each treatment's clinical effectiveness. The evidence presented for ponesimod is no different.

Comment 7 Factual inaccuracy (ACD 3.7 – page 9): Network meta-analyses

In section 3.7 NICE notes that "*to reduce heterogeneity in study design, at technical engagement the company suggested pooling interferons*". We would like to clarify that at technical engagement the heterogeneity and clinically implausible results produced by some of the interferon trials (namely INCOMIN and ADVANCE) were discussed with the ERG, and the suggestion to conduct a pooled interferon NMA came from the ERG. In line with this suggestion Janssen carried out a class-based NMA as the revised base-case for ACM 1.

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Comment 8 Additional Comment (ACD 3.9 – page 10): Cladribine in highly active RRMS

In section 3.9 if the ACD, NICE notes "*cladribine had a substantially higher treatment effect for 6-month confirmed disability accumulation than other treatments in the network meta-analysis for the highly active subgroup. It noted that this estimate had wide credible intervals, indicating a high level of uncertainty. The committee noted that because 6-month confirmed disability accumulation is a key driver of the model, this estimate also had a large impact on the cost-effectiveness estimate of cladribine*". We wanted to reiterate that there is uncertainty in the clinical data for cladribine and in addition, highlight that in the treatment of highly active RRMS induction treatments such as cladribine will not be the most appropriate comparator to ponesimod as it will most likely be fingolimod.

Comment 9 Clarification (ACD 3.10 – page 11): Methodology of pooled NMA

In the ACD, NICE notes "*It also understood that the company had excluded several trials that compared interferons with each other from the pooled network*" – Janssen would like to clarify that the interferon vs interferon trials were not excluded by Janssen out of choice, but instead because it was not possible, methodologically to incorporate interferon vs interferon trials since they did not provide any comparative data.

Comment 10 Clarification (ACD 3.11 – page 12): Evidence of serious and rare adverse events

In the ACD, NICE discuss that "*the committee considered that further data would be needed to fully establish ponesimod's safety profile*". Janssen would like to reiterate the availability of up to 10-years' worth of data for ponesimod from the phase 2 trial and that the phase 3 study is over 2-years long (108 weeks) which is a significant amount of data for a new MS DMT. In comparison to other DMTs which were appraised by NICE, the ponesimod trials report some of the longest safety data presented to a Committee, when the Committee have always previously been able to recommend comparator treatments.

Comment 11 Clarification (ACD 3.12 – page 13): Long-term efficacy

In section 3.12, NICE discuss that, "*the committee considered that longer-term efficacy is difficult to establish and extrapolate from short-term trials used in the network meta-analyses, the outputs of which have broad credible intervals*". We appreciate that there are challenges in the data for MS, however we would like to highlight again the network data and trials being reviewed by the Committee are no different for ponesimod, than for other previous appraisals. Just this year (2021) the NICE Committee met to conclude on the appraisals of ofatumumab (NICE, 2021) and ozanimod (NICE, 2021). Furthermore, we would like to reiterate the long-term phase 2 data that is available for ponesimod, in addition to over 2 years of phase 3 data.

Comment 12 Factual inaccuracy (ACD 3.15 – page 15): Treatment sequencing for SPMS

In section 3.15, NICE note that "*the company did not present any analysis that allowed for treatment switching or sequencing*". Janssen would like to clarify that for the original submission we accounted for sensitivity analysis in the model, which allowed active RRMS patients to move onto one treatment (cladribine) and similarly patients with highly active disease were allowed to move onto natalizumab. During technical engagement, the ERG noted that this was a "*simplifying approach*" and that "*modelling*

subsequent treatment effects introduced additional uncertainty". While we appreciate the rationale stated by the ERG during technical engagement and understand in line with Committee comment that "*an economic model that can simulate treatment sequencing would be complex to construct*", we note that we did indeed attempt to factor treatment sequencing into the economic model to allow for a more realistic treatment follow-on. However, as already stated by the clinical experts the subsequent treatments which patients receive is usually determined by the treatment they are currently on in addition to several individualised factors, making treatment sequencing in the model highly complex.

Comment 13 Error in the ERG/Committee economic model revision

We identified one issue that was introduced when the model was modified in the application of the hazard to risk ratios. The issue was in the Calculations – Primary and Calculations – Secondary sheets, in the tables containing EDSS transition probabilities after the application of treatment effects. These calculations had been adjusted in the ERG revision of the model. The adjusted calculations did not account for cases in which the sum of regression or progression probabilities from a given EDSS state equal 0 and would output a #DIV0! error in these cases. We found this issue when switching from the British Columbia source to Dimethyl Fumarate & London Ontario source in sheet 2.4, as the sum of the regression probabilities from both EDSS 8 and EDSS 9 are equal to 0 when using the Dimethyl Fumarate & London Ontario source. We have added a conditional statement in the calculations to account for this case, preventing the #DIV0! error. This issue does not affect the results, except that for some values for the initial distribution among EDSS states (including using the UK MS RSS for specifying the initial population characteristics), the results will not calculate, and the model will output #DIV/0! errors.

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Ponesimod for treating relapsing multiple sclerosis [ID1393]

Consultation on the appraisal consultation document – deadline for comments end of day on 25 October 2021. Please submit via NICE Docs.

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

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Ponesimod for treating relapsing multiple sclerosis [ID1393]

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	Do not paste other tables into this table, because your comments could get lost – type directly into this table.
	Notes on this submission: In light of NICE's initial decision on ponesimod, we asked people with MS to share their experiences of DMTs generally and their expectations of ponesimod with us. We have also used some feedback we have received from previous engagement with the MS community.
1	**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. In general, the MS community are positive about the potential for a further oral treatment option, not only for its simplicity but also as a means of reducing the complications from regular injections. Not every person with MS is suitable for or will have a preference for an oral option, but people with MS often tell us of a preference for tablets. 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. One person with MS told us "*My DMT journey began with injections. Being diagnosed with MS was mind blowing and then on top of this I had to come to terms with injecting. It felt like a lot to deal with and honestly impacted my compliance to my medicines. After 2 injectable medicines failed to control my MS/impacted my liver, I was given an oral DMT. My level of compliance has significantly increased. It's much easier to take a capsule. When you are not feeling well, when days aren't bright then having to perform an injection seems intolerable. But I am able to take a capsule… when assessing new medicines being made available to people like me, please remember that the ease of taking them matters".* Another person with MS said " *An oral tablet would be easy for me to administer myself which wouldn't be possible if an injection were required. It would mean I could maintain some better quality of life with the chance of enjoying the things that make my life more enjoyable and manageable for longer. It would allow me to continue to live independently in my home without relying on carers which is a very scary thought for me."* Others agreed with this and explained why they would prefer an oral therapy: *"Knowing someone who has injected Avonex Interferon for many years I can say that injecting once a week takes its toll on mental wellbeing"* *"I have been using Rebif since 2008. I inject three times per week and I have developed lesions in some injection site areas. I am concerned that I will no longer have sites in which to inject"* *"I would love a tablet instead of an injection that takes about 8 hours to do. "* *"Injecting was so difficult, to hold the needle, to aim for the right area, and then the general pain and irritation at the injection sites were nasty. I would've given anything to have tablets instead."* *"Life revolved around the correct times to take the injection out the fridge, remember if it*

	was injection day, inject correctly, and how I'd feel after. It was like clock watching! Going away anywhere involved taking the correct amount of injections with me." 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. A 2014 study (1) comparing hypothetical choices of oral versus other DMTs showed that oral options were preferred over injections by 93% of patients, when frequency of treatment use and of side effects were held to be constant, although preferences switched to injections if the oral options had to be taken three times daily and injections only once per week. Importantly, if approved, ponesimod 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 relapsing MS group represents a clear unmet clinical need. **References:** 1. Utz et al., 2014. Patient preferences for disease-modifying drugs in multiple sclerosis therapy: a choice-based conjoint analysis (nih.gov)
2	**People with MS value choice in treatment options** Decisions on which DMT to use can be complicated and are determined by a wide range of factors including effectiveness, eligibility, the level of side effects, the method and frequency of administration, as well as individual lifestyle factors. Individual preferences and weight attached to different factors can be as variable as the condition itself. The wider the range of safe and effective treatments, the greater the choice for people with MS and the greater the chances than an individual will find a DMT that works for them. One person with MS told us- *"Deciding to take DMTs is often not a simple decision. It can require you to perform injecting yourself, it may require infusions in hospital and it will definitely require you to weigh up the risk/benefit of the potential impact to your conditions journey vs the potential side effects.* *Effective treatments that are both easy to take and tolerate are very important to made available to patients. Dealing with MS means we have the physical impact to deal with but we also have the mental toll to handle. Our medicines should not be part of this burden.* *Personally, I have declined certain DMTs because of the serious side effect risk even if they have good clinical profile because I can't risk anything else to deal with.* *I think when assessing new medicines being made available to people like me, please remember that the ease of taking them and the ease of tolerating them matters."* In response to the news of NICE's initial decision on ponesimod, some people with MS wrote to us about the general need for more treatments, given how severe the condition can be. One person said "*Please don't stop any new medicine for MS- we need to try as many*

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	as we can. MS has robbed me of my life. I've had to stop work which I loved, and driving. The lockdown was terrible and I can't get out of house on my own. Walking is bad and painful. It's soul destroying. "
3	**Ponesimod was effective for people who were on the trial** In response to our news story about NICE's initial decision on ponesimod, the MS Society was contacted by six people with MS who have taken part in one of the clinical trials of this treatment. Strikingly, all of these people described what they saw as very good responses to the treatment, and felt it should be approved. Some of these people wished NICE to be informed that they would be willing to provide any further information required for the appraisal. **Person A** "I have been on the medication since 2010. I had 6 relapses prior to enrolling on the study, and have had none since. My EDSS score of disability was 1.5 at baseline in September 2010 and was 1.5 in September 2021, showing that I am in the same position. I have had no relapses in 12 years, further, any sensory and muscle related symptoms have disappeared. I feel cured. This is a remarkable drug, and has given me freedom to live my life. I have had no days off sick for MS in 12 years. I work full-time, and I am a father of two boys. I walk, run, cycle and we're going skiing in February. If you wanted a walking advert for Ponvory, then it is me. I believe that the ability for Ponvory to effectively stop MS in its tracks, the ability to reverse symptoms, to prevent disability, and for patients to remain relapse free for many years is nothing short of amazing. It has the potential to transform people's lives. For the newly diagnosed it offers stability of the life they're living today, and for those with some level of disability, it offers hope that they won't get worse, and might actually improve. It should be the first line of defence offered to patients upon diagnosis." **Person B** I have heard today that the drug Ponesimod has been initially refused by NICE. I have been a participant in this drug trial since…2010 and wish to share my experience. I am very disappointed with this news. I was diagnosed with RRMS at the age of 47 in 2010 and after 11 years of being on the drug, I understand I am according to my Consultant…."doing very well". I lead a full and happy life and although I have some sensory issues and suffer from fatigue from time to time, I am fully mobile and my MS does not stop me doing anything that I wish to do. Ponesimod is a ground breaking drug that could help MANY people with RRMS and surely the opportunity cost of the saving in cost of the future health care of people with RRMS must be weighed against the cost of providing the drug that could make such an enormous difference to the lives of many. I have experienced no side effects and have found the ease of taking a tablet each day is helpful. Above all I have hope that although I understand that the progressive nature of this neurological condition makes it likely that I will slowly decline, I cling onto hope that I may not require a wheelchair in the future. I hold onto this hope and

	can honestly say hand on heart, that I believe Ponesimod has been the reason for my good health. What price does NICE place on the quality of life of someone with MS? What happens to the participants who have given up 11 years of their life for endless hospital appointments in the hope that they may make a difference to the lives of others with RRMS in the future? Where are the ethical considerations in this also and will we be able to continue on this drug? I await further information and am absolutely devastated with the news announced today" **Person C** "I have heard today that NICE does not recommend Ponesimod (Ponvory) as an NHS treatment in England and Wales....my personal experience has been exceptional. In the year before starting the drug I suffered drop foot, double vision, numbness on my face and severe fatigue. I started the drug a few months after my last relapse and haven't had a relapse since… that's 11 years!! Your argument against the drug is that you are 'unsure of Ponesimod's ability to slow down disability progression' and therefore, 'ponesimod is not considered to be cost-effective for the NHS'. This has been an 11 year trial and for me to have no relapses is incredible. I do not need to claim disability benefits because of the effectiveness of this drug. …I look to my future and obviously consider that my condition may worsen but hope that I; do not lose my voice, my mobility or my sight to name but a few devastating effects that this disease can bring. I truly believe that Ponesimod has been the reason for my continuing good health. What price does NICE place on the quality of life of someone with MS? Participants have selflessly for the last 11 years given their time for hundreds of hospital appointments in the hope that they may make a difference to the lives of others with RRMS in the future? Every bit of feedback I have had about this drug has been nothing but positive and I will be devastated if it isn't approved" **Person D** "I was very surprised and concerned to hear of NICE's recent decision about Ponesimod. As someone who has been taking this medication I thought that you may be interested to hear of my experience. I was diagnosed with MS early in 2010, and have been on the Ponesimod trial since August of that year. I had had three relapses, and my MRI showed in excess of 10 lesions. Since starting Ponesimod I have had no further relapses, and my recent MRI showed no new lesions compared to 2010. My fatigue levels are also exactly the same as they were 11 years ago. NICE are concerned about Ponesimod's effect on disability progression. In terms of disability, I would say that I am essentially unchanged from when I was diagnosed, and in some ways have actually improved - for example, I no longer get "foot drop" after walking

	for 20 minutes. I think that most people, even those who do not have MS, would not be able to say the same after 11 years. In addition to my personal experience, the others I have met on the trial all report similar outcomes" **Person E** "Before this medication I was having relapses approximately every three months. From losing my sight in one eye to being unable to walk for a periods of time due to numbness and loss of sensation, to name but a few adverse relapse conditions I've experienced since being diagnosed with MS This medication has been a godsend and has enabled me to build my own business and live my life to the full. Since being on this medication for over a decade now I cannot sincerely remember any time when I've had a MS relapse or any other adverse affect from the actual medication. I am able to work, provide for my family and contribute to society I do believe things would of all been different had I not been lucky enough to go on this trial Working in the city centre and dealing with hundreds of people every week none of them would think I had anything wrong with me which truly proves the effectiveness of the medication and if all people with MS were in my similar physical, mental and well-being state of health and mind then I think they would all want to be on the medication. Having seen the severe impact MS can have some people's health, well-being and quality of life I feel very fortunate." **Person F** "You will by now have been presented with all the scientific data about Ponesimod and have scrutinised all the facts and figures. I can add nothing to this; I can only offer an account of what Ponesimod means to me and how it has impacted on my life. I was initially diagnosed with MS in 2009/2010, first presenting in … 2009. … Luckily my consultant was involved in the clinical trial for Ponesimod that was about to commence and i was offered a place on it. I started on Ponesimod clinical trial in June 2010. I don't know if I was on the medication or placebo at the start of the trial - certainly, I had no relapses, although I continued to experience fatigue, some physical and cognitive distress. I was still consumed by the memory of that horrible episode, the fear of it recurring, of how my future could be impacted. Within a couple of years on the trial I began to realise that I was feeling increasingly stable. That I could begin to imagine a normal life for myself, a normal future. Ponesimod is so easy, so unobtrusive. Just a simple pill taken every day. As I was accepted on to the trial so soon after diagnosis, I have no experience of other drugs or treatments, so I cannot offer a comparison, but I can say that the simplicity and efficacy of Ponesimod has allowed me to get on with life without MS completely dominating it. No drips, no injections. Just one little pill and I'm good to go. I have had zero relapses, very few minor episodes, no work days lost, no impact on my daily life since being on this drug, and no side effects. My initial EDSS score was 1.5; it has since improved to a score of 1. I have experienced a return of sensations in digits that I had lost since the initial episode, and although I still experience intermittent symptoms such as spasms, these are increasingly

	rare and mercifully brief. I feel generally well in myself, in fact, I feel better than I did before my diagnosis, which suggests to me that I may have been suffering from MS for some time previous to my crisis. Sometimes I feel like a fraud when I say I have MS; you honestly wouldn't be able to tell. But every day I take my pill I offer a silent prayer of gratitude that I no longer experience what I never allow myself to forget: the pain, the fatigue, the mental confusion - but above all the fear. For my mobility, my employment, my independence, my personal relationships, my mental state. Those specific fears have now dissipated. Now my fears are of what will become of me if Ponesimod is no longer available to me. I know there are other treatments available, but this one is so effective. It has given me back the confidence to face the future and to imagine and plan for a normal life. I know it can do the same for others. I'm sure that you can see the science and evaluate how successful Ponesimod is in the treatment for relapsing MS, but what the data cannot tell you is how important it is for the mental and emotional wellbeing of us, the MS sufferers who have been fortunate enough to have had the opportunity to trial this drug"
4	**The impact of effective MS treatment options on carers and wider society** The wide-ranging impact of MS, its progressive nature, the relatively young average age of onset and the many years people spend living with the disease all mean that any effective treatment has an large effect not only on individuals, but also on carers and at a societal level. It is difficult to capture this in standard cost benefit analysis. People with MS often need support from family and/or friends to help them manage the impact of having MS and help them maintain their independence. This includes support with everyday tasks like washing and dressing and getting out and about. As disability progresses the need for this support increases and the impact on carers can be greater. Our 2019 My MS My Needs survey (1) showed that 40% of respondents with a need for care and support relied on some degree of unpaid care from their family and friends. The effect MS has, not only on the person's life that has the condition, but also on those close to them is significant. Any effective treatment for MS would lead to more people remaining independent for longer and therefore delay the point when they may need to rely on support from carers. In turn this would lead to carers experiencing greater independence allowing them the space to focus on their own health and wellbeing. One carer told us "I have cared for my wife for over 30 years with MS. At first she had a slight limp, but over the years has gradually lost mobility. Now she constantly needs walking aids, and has not enough energy for more than about 20 feet. Last year she had a fall and was in hospital for 3 weeks. In April she had a second fall and is now in constant pain. Anything that can slow the disease progress further will help stabilise her decline, and greatly improve my own outlook, which currently looks bleak." Another explained "I now struggle to do most things that make life bearable. I fall a lot, can walk for only a few minutes and have lost all confidence and sense of self worth. My husband sees MS before he sees me and treats me as a patient and we mourn what we once were."

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	References: 1. My MS My Needs survey 2019: UK findings -MS Society External template
5	**Relapse rate and disability progression** Ponesimod 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 teriflunomide. Ponesimod was found to be superior to teriflunomide on no evidence of disease activity (NEDA) status. Rates of confirmed disability accumulation 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. 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 the CRIMSON study (2) which aimed to improve understanding of how people with relapsing MS weigh up the pros and cons of different DMTs. It demonstrated the various and interrelated factors informing a person's choice of treatment. It was concluded that 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. Clearly, longer term outcome data is required to assess ponesimod's effects on disability progression relative to its comparator, 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. **References:** 1. 2014, The UK patient experience of relapse in Multiple Sclerosis treated with first disease modifying therapies - Multiple Sclerosis and Related Disorders (msard-journal.com) 2. The CRIMSON Study, 2018. Understanding treatment decisions from the perspective of people with relapsing remitting multiple Sclerosis: A critical interpretive synthesis - White Rose Research Online
6	**The value of a treatment proven to reduce fatigue** Fatigue is one of the most commonly reported invisible symptoms by people with MS, with many finding it's the symptom that affects them most. Fatigue can have enormous, varied effects on daily life which may not be clearly reflected by a person's EDSS score. In clinical trial, ponesimod was significantly better than teriflunomide in scores of MS related fatigue,

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	as reported by patients through the new Fatigue Symptoms and Impacts Questionnaire-Relapsing Multiple Sclerosis (FSIQ-RMS) outcome measure. Whilst we understand that ponesimod cannot be compared with any DMT other than teriflunomide on measures of fatigue as the FSIQ-RMS measure was not used in prior clinical trials, we would emphasise the scale of the unmet need for any treatment proven to reduce levels of MS related fatigue.
7	**Family planning** MS is the most common disabling neurological condition of young adults. Many who have MS are diagnosed in their twenties and thirties, at a time when people may be considering starting a family. The preliminary recommendations may therefore have a different effect on younger women and those considering pregnancy than on the wider population, with age and pregnancy both being protected characteristics. A 2020 study (1) reported that women with RRMS who are considering future pregnancy prefer to use DMTs with more favourable reproduction-related attributes, even when not trying to conceive. The study showed that reproductive issues also influenced people's preferences for DMT attributes that were not directly related to pregnancy, with preferences dependent on the life circumstances in which choices were made. The short half-life of ponesimod may also impact on family planning for men. One person we spoke to emphasised family planning as a key factor for him in treatment choice, saying "as I yet do not have children and I want to become a father, information about the DMT's impact on fatherhood is important."

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- 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 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.

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- 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.

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	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Multiple Sclerosis Trust
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
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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.
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 ponesimod as an NHS treatment for active relapsing remitting MS. We note that the committee recognises that ponesimod reduces the number of relapses compared with teriflunomide but finds that ponesimod'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. Having an additional first or second-line treatment would offer people with MS and clinicians greater scope for personalised treatments.
2 General comment	**Ponesimod would be a valuable additional oral treatment** Ponesimod would be a valuable alternative to the two oral treatments currently used for active relapsing remitting MS: dimethyl fumarate and teriflunomide. Ponesimod 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. Ponesimod 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**

[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.

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	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 was associated with a higher relapse rate and higher discontinuation rate due to disease breakthrough[5]. • **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 General comment	**Earlier access to a more effective oral treatment** There are currently no oral drugs routinely available as first-line treatments for people who have only had one relapse in the last two years. Both dimethyl fumarate and teriflunomide require people to have 2 significant relapses in last two years, which carries the risk of accumulating additional disability from additional relapses and “silent” MS activity resulting in further lesions. People with MS are increasingly aware of the significance of reducing or eliminating signs of sub-clinical disease activity in improving long term outcomes. There is a growing recognition that regular clinical evaluation and regular MRI scans are required to fully assess MS activity and response to disease modifying drugs. The majority of people with relapsing remitting MS are eager to start treatment with one of the disease modifying drugs and aware of the importance of starting treatment as soon as possible after diagnosis. Waiting for a second relapse to happen in order to start a treatment is a major source of anxiety. Access to ponesimod would allow people with MS to start treatment earlier and with a more effective treatment than beta interferons and glatiramer acetate. There is strong clinical evidence that early and more effective treatment results in better long term disability outcomes.
4 3.4	**Ponesimod’s effect on progression of disability is unclear** **We urge the committee to reconsider their conclusions on disability progression in the context of previous NICE appraisals for disease modifying treatments.** In clinical trials, ponesimod showed a numerical improvement in confirmed disability progression

[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

compared to teriflunomide, although this was not statistically significant. The Committee has previously concluded that teriflunomide may have a beneficial impact on accumulation of disability (TA303). This leads to the conclusion that ponesimod significantly reduces disability progression compared to best supportive care and is at least as effective as teriflunomide, if not more effective.

A recent study found that it can take up to 16 months for a disease modifying drug to have a full clinical effect on disability progression[7]. In the case of fingolimod, the therapeutic lag was 11 months. This would suggest that a two-year clinical trial is not long enough to see a significant difference between active comparators, particularly for six month confirmed disability progression.

A review of NICE FADs (see below) shows that in previous appraisals, the Committee has recognised that the majority of disease modifying treatments significantly reduce disability progression when compared to best supportive care but not when compared to active comparator.

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–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

[7] Roos I, et al. Delay from treatment start to full effect of immunotherapies for multiple sclerosis. Brain 2020; 143(9): 2742-2756.

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	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.
5 General comment	**Mechanism of action** Ponesimod 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. Ponesimod 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, ponesimod might be expected to cause fewer side effects compared to fingolimod. Approval of ponesimod would allow clinicians and patients to access this proven, very effective mechanism of action as a first line treatment.
6 General comment	**Conclusion** Ponesimod would be a valuable additional treatment for active relapsing remitting MS. Once daily oral route of administration means that ponesimod can be taken at home, eliminating potential delays in starting treatment which have occurred with other disease modifying drugs which require access to outpatient infusion clinics. Overall, this route of administration minimises demands on NHS services. Fatigue is one of the most common and debilitating symptoms of MS and can be one of the most challenging to manage and treat. Ponesimod's potential for improvement, or at least stabilisation, of fatigue levels will be a significant advantage for people with MS. Ponesimod is rapidly eliminated and lymphocyte counts return to normal range within 1 week. This will be beneficial for people needing vaccination, in cases of serious infection or for women who want to start a family. The impact of certain disease modifying drugs (particularly ocrelizumab, ofatumumab, fingolimod, alemtuzumab) on the effectiveness of Covid vaccination has been an increasing cause of concern for patients and clinicians. Titration of the first dose of ponesimod minimised first-dose cardiac effects; people with MS will not need to be monitored in a hospital clinic while taking the first dose, as is required for fingolimod. 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.

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

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	Merck Serono Ltd (Merck) noted Section 3.9 of the Appraisal Consultation Document (ACD): *"The committee noted that cladribine had a substantially higher treatment effect for 6-month confirmed disability accumulation than other treatments in the network meta-analysis for the highly active subgroup (see section 3.7). It noted that this estimate had wide credible intervals, indicating a high level of uncertainty. The committee noted that because 6-month confirmed disability accumulation is a key driver of the model (see section 3.12), this estimate also had a large impact on the cost-effectiveness estimate of cladribine. The clinical experts did not consider that cladribine shows a substantially greater treatment effect than other comparators in clinical practice, which is supported by results from the full population analysis. The committee considered that this anomalous result needs exploring further, particularly if there were any characteristics from the cladribine trials which could explain this."* As the manufacturer of Cladribine Tablets, Merck would like to respond to this section of the ACD. Firstly, we acknowledge that the redactions in the company submission and other relevant documents mean that we cannot comment on the specific NMA results described for Cladribine Tablets. Secondly, we wanted to highlight that there is no detail provided on the questions asked to clinical experts about Cladribine Tablets, so it is hard to comment on the specific opinions given here. Further detail on how this expert opinion was obtained would be valuable to support interpretation of this section. In response, Merck would like to provide analysis/data for Cladribine Tablets to support the efficacy in the relevant RRMS subpopulations. Specifically, this will cover: A. The highly active disease (HAD) subgroup as defined by NICE: Patients whose disease progressed or remained unchanged within the last year despite having previous disease modifying treatment B. The broader HAD subgroup, in line with similar definitions from the ponesimod clinical trial (OPTIMUM) and in line with the Cladribine Tablets marketing authorisation[1]: Patients with ≥2 relapses in the year prior to study entry whether receiving a disease modifying therapy (DMT) or not; and patients with ≥1 relapse during the year prior to study entry while receiving a DMT with ≥1 T1 gadolinium-enhancing or ≥9 T2 lesions o This definition of highly active RRMS is broader than the NICE definition, and thus also incorporates patients with rapidly evolving severe (RES) RRMS as defined by NICE. o This subgroup is also relevant for this response, as in the NMA provided in the company submission, trials were selected for inclusion in the analysis based on their alignment with the definition used in the OPTIMUM trial. As described in the company submission: "*For all three efficacy outcomes, it was found that a network containing all relevant comparators would not be possible, due to a lack of reported subgroup data for some outcomes. To ensure full network connectivity, an assumption was made that the outcomes for the ITT population were equivalent to*

those of the HAD RRMS subgroup in these trials, similar to analyses presented in TA533." In TA533 the committee concluded that this assumption led to uncertainty in the clinical effectiveness of ocrelizumab versus comparators in the HAD and RES subgroups.

Merck would also like to clarify the distinction between the two definitions of HAD. The ponesimod ACD, and the discussion about the efficacy of Cladribine Tablets in this ACD, refers to the narrower NICE definition of HAD as stated in point A above. However the marketing authorisation for Cladribine Tablets corresponds to the broader HAD subgroup, as defined in point B above.[1] This broader definition is also aligned to the NICE recommendation for Cladribine Tablets, as it also includes the RES subgroup (TA616).

Brief summaries of the published studies demonstrating efficacy of Cladribine Tablets are provided below:

Giovannoni et. al. 2019. Efficacy of Cladribine Tablets in high disease activity subgroups of patients with relapsing multiple sclerosis: A post hoc analysis of the CLARITY study[2]

The efficacy of Cladribine Tablets in the broader HAD subgroup was reported in Giovannoni et al.,[2] which was a post hoc analysis of the pivotal CLARITY Phase 3 study. Outcomes of patients randomised to Cladribine Tablets 3.5 mg/kg (n=140) or placebo (n=149) were analysed for the definition described above in the broader HAD subgroup. Cladribine Tablets reduced the risk of 6-month-confirmed CDP by 82% (risk ratio: 0.38 [95% CI: 0.07-0.43; p=0.0001]), and 95.5% of patients were free from 6-month CDP with Cladribine Tablets, compared to 77.7% with placebo.[3] NEDA-3 (no evidence of disease activity; defined no relapses, no 6-month sustained change in EDSS and no new T1 gadolinium-enhancing lesions or active T2-weighted lesions) was also achieved in 44% of patients with HAD who received Cladribine Tablets compared to 9% with placebo, and 77% were relapse free, compared to 50% with placebo.[2]

This analysis demonstrates that patients identified within the broader HAD criteria showed clinical and MRI responses to Cladribine Tablets, in a group of who may be at risk of poor long-term clinical outcomes.

Berardi et al. 2019. Estimating the comparative efficacy of cladribine tablets versus alternative disease modifying treatments in active relapsing–remitting multiple sclerosis: adjusting for patient characteristics using meta-regression and matching-adjusted indirect treatment comparison approaches[4]

This publication reported on the methodology and results of a study which estimated the comparative efficacy of Cladribine Tablets versus alternative DMTs – fingolimod, natalizumab, alemtuzumab and ocrelizumab – in adults with active RRMS subgroups, using meta-regression to provide sub-population specific estimates of drug effect. Of note, this study provided results for the broader HAD definition (in line with Giovannoni et al.[2] and with previous clinical trials, including OPTIMUM), as well as in the specific HAD population defined by NICE. In this publication, the NICE definition of highly active disease was referred to as the sub-optimal therapy (SOT) subgroup. A Bayesian meta-regression analysis was conducted to provide HAD-, RES- and SOT-specific estimates of the relative effect of Cladribine Tablets compared to the relevant DMT comparators. The focus of

	the publication is on the key highly efficacious comparators of alemtuzumab, natalizumab, fingolimod and ocrelizumab. The comparative effectiveness data was generated by running a series of models with adjustment for baseline risk that were fitted to data from the ITT cohorts of trials identified in a systematic literature review (SLR). The analysis was based on methodology for meta-regression on baseline risk published by the NICE Decision Support Unit. More detail on the methodology can be found in the study publication and supplementary appendix.[4] The results of the meta-regression analysis showed significant overlap in the credible intervals for the hazard ratios (HRs) of 6M-CDP, with no therapy statistically dominating in terms of efficacy. At the point estimate level, Cladribine Tablets were predicted to be more efficacious in the broad HAD population than fingolimod (HR: 0.77, 95% CrI [0.40; 1. 44]), alemtuzumab (HR: 0.92, 95% CrI [0.40; 2.23]) and ocrelizumab (HR: 0.87, 95% CrI [0.36; 2.02]). However, a similar result was not found for the comparison of Cladribine Tablets and natalizumab (HR: 1.08, 95% CrI [0.53; 2.21]). In general, similar trends were seen for SOT and RES subpopulations. Consequently, the results of these meta-regression analyses suggest that Cladribine Tablets have comparable efficacy to alternative high-efficacy DMTs in active RRMS, specifically in patients diagnosed with HAD, RES or SOT. These findings also support previous network meta-analysis that suggested Cladribine Tablets were a comparatively effective and safe alternative to other DMTs in RRMS patients with high disease activity. Note, ponesimod was not included in this comparison. In conclusion, this rigorous analysis confirms a need to adjust for population characteristics when estimating relative treatment effects in RRMS to account for the heterogeneity across clinical trials, particularly when these are used to re-estimate absolute treatment effects (such as in health economic analyses), as the resulting effect sizes can differ across sub-populations. The ponesimod ACD notes that the ponesimod NMA used unadjusted effects from each of the included trials, and the company did not calculate effects using meta-regression: in effect, therefore, the company have assumed homogeneity in the trial evidence, despite evidence that this is not the case. As noted in the ACD, this makes the results from the company's network meta-analyses highly uncertain and therefore should be interpreted with extreme caution. Merck believe the data provided above support the clinical efficacy of Cladribine Tablets in the broad HAD and NICE-defined HAD (referred to as SOT in Berardi *et al*. 2019) subgroups. As noted above, the Berardi 2019 study showed that no therapy statistically dominated in terms of efficacy, however at the point estimate level Cladribine Tablets were more efficacious than most of the comparators. The result of Berardi 2019 could be interpreted to align with the clinical expert opinion in the ponesimod ACD, as clinicians did not consider that Cladribine Tablets showed a ***substantially greater*** treatment effect vs comparators, and superior efficacy of Cladribine Tablets in the Berardi 2019 study was not statistically significant. However, we cannot be certain as we are not able to review the exact NMA outputs due to redactions in the committee papers, and the lack of detail on the clinical expert opinion further prevents interpretation. The committee considered that this anomalous result needs exploring further. We have presented here the results of a separate published indirect treatment comparison (albeit without ponesimod included) which adjusted for population characteristics when estimating treatment effect. As such, we believe that it may be worth exploring the methodology of the company's NMA which led to this anomalous result, rather than the characteristics of CLARITY, given the lack of an anomalous result

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	for Cladribine Tablets in an alternative indirect treatment comparison. Merck considers that without exploring the company NMA methodology further, it is unreasonable to comment on the efficacy of a particular comparator product and clinical trial characteristics. **References** 1. Cladribine Summary of Product Characteristics. 2. Giovannoni G et al. Mult Scler J. 2019;25:819–87 3. Merck Data on file. CLAD009. 4. Berardi A et al. Curr Med Res Opin. 2019;35(8):1371–1378.

Insert extra rows as needed

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- 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 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.
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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

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Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Since April 2005 Novartis has exclusively licensed glycopyrronium bromide and certain intellectual property relating to its use and formulation from Vectura and its co-development partner, Sosei Heptares. The following inhaled medications are comprised of, or contain glycopyrronium bromide: • Seebri® Breezhaler® (glycopyrronium bromide) (used as a maintenance treatment for Chronic Obstructive Pulmonary Disease (COPD)) • Ultibro® Breezhaler® (indacaterol/glycopyrronium bromide) is used as a maintenance treatment for COPD • Enerzair® Breezhaler® (indacaterol/glycopyrronium bromide/mometasone furoate) is used as a maintenance treatment for asthma uncontrolled with LABA/ICS. Phillip Morris International (a tobacco company) is currently in the process of acquiring Vectura Group plc.
Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	Para 3.2: "…stating it did not consider ponesimod would not be used for secondary progressive multiple sclerosis." The construction of this statement regarding the potential use of ponesimod in SPMS is inaccurate; Novartis suggests this be reworded to "…stating it considered that ponesimod would not be used for secondary progressive multiple sclerosis."
2	Para 3.2: "…agreed to define it" [*i.e.*, highly active disease] "as people whose disease progressed or remained unchanged within the last year despite having previous disease-modifying treatment" This statement regarding the definition of highly active disease is imprecise and potentially misleading in the context of the wording of DMT licences and the NHS treatment algorithm. Please clarify whether the analyses presented for this subgroup required "disability progression" (which is not usually part of the definition of highly active disease) or whether the phrasing "disease progression" was instead intended to cover the occurrence of relapses and/or MRI signs of inflammatory activity, as would be consistent with the subgroup definitions in the DMT licences/NHS algorithm; each of these three potential interpretations of the criteria (one of which is not ordinarily included in the definition) ought to be explicitly defined when describing the subgroup analysis. Please additionally clarify whether the analyses presented required the disease activity and/or progression to have occurred while patients were on treatment or whether the criterion of prior DMT was independent of

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	the occurrence of activity and/or progression.
3	Para 3.9: "The committee considered that this anomalous result" [*i.e.*, cladribine having a higher treatment effect than other DMTs in the subgroup] "needs exploring further, particularly if there were any characteristics from the cladribine trials which could explain this." Novartis agrees with the clinical experts quoted in the ACD and with the Committee conclusion that this result is anomalous and not aligned to the findings of other NICE technology appraisals of DMTs for MS. Novartis would note the approach taken in TA699 where the NMA of the trial ITT populations for each DMT was accepted by the Committee as generalisable to each of the subgroups in the scope, as there is no evidence that subgroup membership is itself a treatment effect modifier. This approach generated effect estimates for cladribine that are in line with the clinical expert opinion quoted in the ACD and would be consistent with the conclusions of a recent prior appraisal.
4	Para 3.10: [re pooling interferons] "Further information on how well alternative approaches to pooling fit the data, and further sensitivity analysis showing the effect of different network meta-analysis assumptions on the cost-effectiveness estimates would be needed." Novartis agrees with the Committee that the principle of pooling interferon data in the NMA (using appropriate statistical methodology) should be explored. However Novartis considers it important to separately analyse the cost-effectiveness of each interferon using the separate confidential net prices to the NHS in the cost-effectiveness analyses.
5	Para 3.12: "The committee noted that many assumptions in the model had been accepted in previous technology appraisals in multiple sclerosis, including: … incorporating a treatment waning effect of 25% reduction in efficacy from years 2 to 5 and a 50% reduction in efficacy from year 6 onward …" Novartis disagrees with this statement and considers it to be a misleading description of the use of arbitrary waning assumptions in prior appraisals. The inclusion of waning assumptions has varied considerably across recent appraisals, with the Committee concluding that no arbitrary waning should be included in the economic model in both TA699 and TA533. Furthermore, in those appraisals where the Committee have included arbitrary waning, the values used have varied considerably. Notably in TA527 arbitrary waning was assumed to apply only from Year 11 onwards (with a straight drop to 50% efficacy). The specific waning assumptions reported in the ACD have therefore only been accepted by the Committee in 2 of the 5 positive NICE recommendations for DMTs in RRMS published since 2018 (TA616 and TA624), which is not the impression given by the ACD text. Novartis requests that the Committee note that Committee preferences as to the inclusion or not of an arbitrary waning assumption, as well as the timepoints and values of any arbitrary waning applied have varied significantly across appraisals.
6	Para 3.12: "However, it acknowledged that a model that can simulate treatment sequencing and variable treatment waning would be complex to construct and difficult to populate because of limited data." Novartis welcomes the Committee's realism as to the data available for modelling, in reaching this conclusion. Novartis supports the acceptance of the well-established model structure for assessing RRMS DMTs.
7	Para 3.15: "The committee concluded that the model did not allow for treatment sequencing that would reflect clinical practice and that including only costs but not the treatment effect of siponimod was not fully consistent." Novartis welcomes the Committee's conclusion and reemphasises that including the costs of siponimod without including its beneficial effect is fundamentally biased and methodologically

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	inappropriate.

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

Name	[redacted]
Role	
Other role	
Organisation	
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?
Not sure

Are the recommendations sound and a suitable basis for guidance to the NHS?
No

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?
Not that I can see

General comments:

"To whom it may concern

Re: Ponesimod drug trial - Janssen

I have heard today that NICE does not recommend Ponesimod (Ponvory) as an NHS treatment in England and Wales and have been asked to write, as a participant in this drug trial since 2010, to share my experience.

I understand that there are only 13 UK participants and that the average results have been extremely good. My personal experience has been exceptional. In the year before starting the drug I suffered drop foot, double vision, numbness on my face and severe fatigue. I started the drug a few months after my last relapse and haven't had a relapse since… that's 11 years!!

Your argument against the drug is that you are 'unsure of Ponesimod's ability to slow down disability progression' and therefore, 'ponesimod is not considered to be cost-effective for the NHS'. This has been an 11 year trial and for me to have no relapses is incredible. I do not need to claim disability benefits because of the effectiveness of this drug.

When reading through your paper for approving Fingolimod (Gilenya) you said '94.1% of all patients treated with fingolimod had no disability progression after 3 months'. This trial has been 11 years and could surely show how much disability progression there has/has not been, thankfully none in my case.

I look to my future and obviously consider that my condition may worsen but hope that I; do not lose my voice, my mobility or my sight to name but a few devastating effects that this disease can bring. I truly believe that Ponesimod has been the reason for my continuing good health. What price does NICE place on the quality of life of someone with MS? Participants have selflessly for the last 11 years given their time for hundreds of hospital appointments in the hope that they may make a difference to the lives of others with RRMS in the future?
Every bit of feedback I have had about this drug has been nothing but positive and I will be devastated if it isn't approved.

As a footnote I have also noticed that The European Commission has approved Ponesimod (Ponvory) which makes me feel even more sad.

Kindest regards.

[redacted]

Name	[redacted]
Role	
Other role	
Organisation	UKMSSNA
Location	
Conflict	
Notes	

Comments on the ACD:

Has all of the relevant evidence been taken into account?

"The UKMSSNA would like NICE to take into account the Pharmacokinetics of Ponesimod and its affect on Multiple Sclerosis Patients. Ponesimod has a short half-life and therefore unlike some other treatments for Multiple Sclerosis it is eliminated from the body quickly and the bodies normal immune response can return within seven to eight days. This is beneficial for several situations such as a patient wanting to start a family, change to another medication or if the patient has other health problems. Ponesimod has no active metabolites this means that it has less interactions with other medications. Patients with Multiple Sclerosis are often on medications to control their symptoms and due to the younger cohort of patients may also be taking medication for contraception. The UKMSSNA feels that because of the cohort of patients that Multiple Sclerosis affects (younger adults) these are benefit of Ponesimod that other disease modifying therapies do not have and these benefit are desirable for patients who wish to have control over their treatment and life.

The UKMSSNA would like NICE to consider the effects of Fatigue on Multiple Sclerosis Patients. Ponesimod is the first disease modifying therapy to show data that suggests a statistically significant reduction in fatigue levels. The UKMSSNA would like NICE to acknowledge that fatigue is a disabling factor in Multiple Sclerosis suffers. Studies suggest fatigue affects 75-85% of Multiple Sclerosis patients and has a detrimental effect to their psychosocial and physical wellbeing. Fatigue is a common factor in Multiple Sclerosis that is not related to the severity of the disease. Fatigue has a serious implication for a population of patients that are of working age which has a direct financial impact on the individual and the state. There are very limited methods and medications used to manage fatigue. The medications that are available to assist with fatigue are off licence and have poor

efficacy and poor data to support their use. Fatigue management programmes or psychological therapies often have long waiting lists or are only available in certain areas of the country. The UKMSSNA welcomes any medication that could reduce this disabling factor of Multiple Sclerosis and feels that Ponesimod has a dual purpose in the management of Relapsing remitting Multiple Sclerosis.

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

The UKMSSNA would like to argue that Ponesimod has shown efficacy and safety in trials and that if the cost was to be within a price range that NICE found acceptable Ponesimod would offer Multiple Sclerosis suffers a first line oral medication. Ponesimod could improve adherence due to the nature of how this medication is taken compared to other first line competitors and would give patients more choice. Research has shown the importance of early treatment in Multiple Sclerosis to reduce the progression of the disease process and prevent disability. As Multiple Sclerosis advances and disability increases so does the cost to the state and to the individual in terms of care needs, financial cost, inability to work, care givers needs and psychosocial wellbeing of the patient and their family (supporting studies can be supplied to NICE if required). The UKMSSNA believes that starting treatment earlier in the disease course reduces the overall cost of Multiple Sclerosis to the individual and the state.

The UKMSSNA accept that there was no significant statistical difference shown in disease progression between Ponesimod and Teriflunomide, but would like NICE to appreciate that it is difficult to gain data on disability progression in such a short period of time. It is possible that changes in the Expanded Disability Status Score (EDSS) at either of these end points (12 weeks and 24 weeks) could be due to a relapse rather than disease progression. Teriflunomide has been licenced for Relapsing Remitting Multiple Sclerosis since 2014. Since licencing Teriflunomide has proven its efficacy with post marketing real world data, there are a number of studies that reflect this (can be presented to NICE if required). Ponesimod had similar efficacy to Teriflunomide in disease progression in the trial OPTIMUM, this would indicate that it is likely to have a similar outcome in the real world. Another indication of this is that Ponesimod showed in the OPTIMUM trial that it reduced annual relapse rate by 30.5% compared to Teriflunomide and active or new lesions by 56%. Compared to Teriflunomide. A reduction in lesion load or active lesions would suggest a reduction in disease progression and disability.

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

No
The UKMSSNA would argue that Ponesimod has a number of factors that would make it beneficial as a first line treatment for people with Relapsing Remitting Multiple Sclerosis. UKMSSNA would urge NICE to reconsider Ponesimod as a first line treatment of Relapsing Remitting Multiple Sclerosis

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?

No

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	

Comments on the ACD:

Has all of the relevant evidence been taken into account?

I am a patient who has been on Ponvory, formerly Ponesimod, and formerly ACT 128800, for the last 12 years. I am a 45 year old man, married with 2 boys. In the time I have been on the medication, I have ran several half marathons and one whole marathon, in less that 4 hours. I receive treatment through BRAMS in Bristol.

I was newly diagnosed 12 years ago, with mainly sensory symptoms, and a record of an increasing number of relapses in the preceeding 24 months, which had an increasing amount of pain and discomfort, including one episode of particularly painful optical neuritis.

I entered the trial within 6 months of diagnosis.

I have had 12 years of no further relapses, and in addition, any symptoms at the start have disappeared. I have no side effects to the medication. While I am not technically cured, I live my life every day with no restriction whatsoever. I feel as though I am cured.

I work full-time in a global technology company. I have had no days off sick due to MS ever.

This is a remarkable medication, and while every decision has to have a cost-benefit analysis, if you ever wanted a walking advert for this medication, it's me.

It is so easy to administer as an oral drug, there are no noticeable side effects.

Ponvory would introduce a powerful new weapon in the armoury against MS, against people losing their mobility, and taking sick leave, and forcing them into permanent sick pay, housing benefit and other costs to the state. I do not claim any benefits, and contribute a large amount of tax every year. This should be part of your evidence. If you want a case study i am at [rich_j_finch@hotmail.com]

The medication should be the default medication as a first line defence against MS

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

No. I believe there are only a very small number of people on this medication in the UK, and I know most, if not all, of them through BRAMS in Bristol.

We are all fantastic adverts for this medication allowing us to continue working, paying taxes, living life, and not claiming disability allowance.

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

Without knowing the price of the drug which is confidential, and without knowing how it compares to other medications in price, this is hard to answer.

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?

no

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	

Comments on the ACD:

Has all of the relevant evidence been taken into account?

It feels that the consultation has been aimed more at clinicians rather than participants who may have wished too be more actively involved. I also feel that the cognitive side of MS was not taken into consideration in the research. I would like to state that on average my cognitive health has remained good and I believe this is a result off taking Ponesimod.

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

I am not an analyst, but a patient with RRMS. as far as I am concerned as previously stated in comments the opportunity cost of potential care for someone later in life wit RRMS has to be balanced against the cost of the life changing drug that could keep them fit and healthy for longer. These are abstract and indeterminate factors as none of us know that course and pathway of our future but the evidence of being on the drug for me for 11 years is that I consider myself to be fairly fit and well having been diagnosed for this length of time and I have quality of life. Why would I want this potentially to change by being denied this drug in the future>

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

No the recommendations are not sound.
Treatments for RRMS..my experience on Ponesimod is that the number of relapses reduced to zero when I started taking the drug 11 years ago, I believe the progression of my disability has been kept to the minimum and I have a good quality of life. My MS does not prevent me doing something I want to do. I do have to manage my condition and take responsibility for my own symptoms such as eating healthily and exercising sensibly and resting if my body demands it, but I believe that Ponesimod plays a significant part in extending my mobility and future quality of life. What measures are used in terms of time for short term and long term as I could not see this stated in the consultation document (apologies if I have

missed this) How long would 11 years be considered in view of the outcome measures and analysis of results? What is ""AN ACCEPTABLE USE OF NHS RESOURCES"" How much is my life worth? How do you measure clinical evidence and benefit against short term evidence if you have not even listened to the personal experiences of drug trial participants. It is not all about looking at brain scans and EDSS scores. I am a strong advocate for Ponesimod if this has not been previously picked up and believe that my own personal experience counts and hope that as a disabled person, my voice will be listened to and heard.

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

I am less concerned about this aspect of the consultation and do not particularly feel that there has been discrimination. The only point I would make is that as someone with the disability of MS, I would like to feel certain that my viewpoints have been taken into account in the final recommendations and I hope that the initial decision will be overturned.

General comments

Treatments for relapsing multiple sclerosis include many disease-modifying treatments. These aim to reduce the number of relapses, slow the progression of disability, and maintain or improve quality of life.Clinical trial evidence shows that ponesimod reduces the number of relapses compared with teriflunomide. However, ponesimod's effect on disability progression is unclear. Comparisons with other disease-modifying treatments are limited by uncertainties in the clinical evidence.

My experience of disability progression is that I have remained stable in terms of my RRMS since I started taking the drug and it has enabled me to have a quality of life I did not think was possible. My EDSS score has remained low ..between 1-3 I believe for 11 years. How long does NICE consider long term progression to be...11 years of being on the drug is in my humble opinion quite a long time of my life. What dies NICE consider an acceptable use of resources..spending money on a drug that potentially changes lives of someone with RRMS, or spending money on their future care because they have been denied the drug that could help them. These opportunity costs could include physio, OT, personal care, nursing, neurology, MRI scans, mental health services. Ponesimod is a life changer for someone with RRMS..I know and it has helped me immensely.

Ponesimod is not recommended, within its marketing authorisation, for treating relapsing forms of multiple sclerosis with active disease defined by clinical or imaging features in adults.

I have been a participant on the Ponesimod drug trial and was diagnosed with RRMS in 2010 and it has been life changing as have had no relapses since my original two in 2010.

This recommendation is not intended to affect treatment with ponesimod 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.

My treatment on Ponesimod has been paid for by drug trial company Janssen so what happens to a participant who has given up 11 years of their life to hundreds of appointments to hopefully help others in the same way I have been helped. Who will fund my future treatment?

Multiple sclerosis is a chronic, lifelong disease with no cure, resulting in progressive, irreversible disability. It has many symptoms, including pain, chronic fatigue, unsteady gait, muscle loss, speech problems, incontinence, visual disturbance and cognitive impairment. Most people have the relapsing–remitting form of the disease, characterised by periods of new or worsened symptoms. The patient experts highlighted that the disease is complex and unpredictable and impacts all aspects of life and can affect carers too. The disease has a higher prevalence in women. Because it is typically diagnosed when people may be thinking about having children, the patient experts highlighted it is important to consider treatments that can be used during pregnancy. The company noted that although ponesimod is not indicated for pregnant women, its short half-life could be helpful for pregnancy planning compared with drugs with longer half-lives. The patient experts also highlighted that oral treatments are generally preferred and that ponesimod is an oral treatment. The committee concluded that despite many available treatments, people would welcome new treatment options for relapsing multiple sclerosis.Comment on section: Treatment pathway, population and comparators

I believe that Ponesimod has been approved by the FDA and also in Europe as a treatment for RRMS, so it seems very unfair that patients in the UK, will be excluded from being offered Ponesimod as a result of BREXIT. An oral drug is easy to take and I believe that the average results of the 13 participants in the UK have been extremely encouraging for 11 years. It is important that NICE considers the personal experiences of participants as well as the clinical evidence. Yes the disease is unpredictable, different for each person and the disease can change in an instant..but all the more reason to try and prevent relapses to keep patients stable and relapse free. What cost does NICE place on people's quality of lives?

The company measured fatigue symptoms using the Fatigue Symptoms and Impacts Questionnaire: Relapsing Multiple Sclerosis (FSIQ-RMS). It considered that OPTIMUM was the first trial to use a validated disease-specific fatigue measure as a prespecified endpoint and show a disease-modifying treatment can stabilise fatigue symptoms. The patient experts highlighted fatigue as an important element of quality of life and that some people would switch to a drug that was shown to act on fatigue. The clinical experts suggested that ponesimod may reduce inflammation which can reduce fatigue. The committee agreed that fatigue symptoms are an important element of the disease and that the FSIQ-RMS has potential to be an important disease outcome measure. However, fatigue was not explicitly included in the model and was instead captured through measuring health-related quality of life by EDSS score (see section 3.12). The committee also noted that because there was no evidence on fatigue symptoms from other clinical trials using the FSIQ-RMS, ponesimod could not be compared with drugs other than teriflunomide. The committee concluded that fatigue is an important outcome measure that was not explicitly modelled in the cost-effectiveness analysis. It was uncertain what effect fatigue would have on cost-effectiveness results without seeing data on how well the comparator treatments reduce fatigue.
Comment on section: Network meta-analysis

Fatigue is one of my most prevalent symptoms of MS as well as some parasthesia, but since being on the drug, I strongly believe that my fatigue wold have been far more severe, and that reduced inflammation has helped this as a result of Ponesimod. Fatigue is a subjective measure as we are all individuals so it is difficult to measure this fairly, but individual experience needs to be listened to. the EDSS does not in my opinion adequately measure fatigue and many of the questions on the scale are not particularly relevant to my MS. Fatigue for me includes such things as mild cognitive impairment, brain fog, slowing up in general activities and reduced ability to carry out normal day to day activities. I would state that it has usually been when I have had abnormal activities that my fatigue has been adversely affected such as when travelling abroad with a time difference (..that was before Covid-19 hit the world) when an unexpected stressful event happens and other such events such as bereavement or loss, which would make any normal person without a condition more likely to slow up in life. List to personal experiences from drug participants about their fatigue as perhaps not sufficient date..Ponesimod makes a massive difference.

The committee considered further analysis was needed to understand the impact of uncertainty on the economic analysis. This would include:further summary statistics and sensitivity analysis on the network meta- analyses, and particularly for interferons:model fit statistics and analysis of inconsistency in the pooled analyses, including trials that compare different interferons with each other in the network, to make direct comparisons between different models possible (see 3.10)a hierarchical class-based model for the interferons, assuming individual treatment effects within a class come from a distribution of effects with a class mean and between treatment variance within classanalysis using updated mortality assumptions informed from new evidencefurther sensitivity analysis that produces more likely modelled outputs, including rate of secondary progressive multiple sclerosis progression and explanation of any inconsistencies of modelled outputs with previous appraisals.

If further analysis is required, then the best way of securing this data is for existing participants to be funded for further longer term research. You can follow me for the rest of my life if it will help me and others. I would not put my life at risk if I believed that there was a safety issue. I have three adult children and I want to be a grandmother who can actively enjoy her life at some point in the future. Please listen to participants and not just clinicians as some clinical observations are subjective and speaking personally I would like to think as someone who is considered to have a disability, that this disability does not rule my life. In my opinion Ponesimod holds the key to however long I may have left in this world. I am 58 and hope to live a long and fulfilled life. Surely NICE wants this for patients instead a life of immobility and misery?

If further analysis is required then I would be happy to continue to be studied as a long term participant on drug trial

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	

Notes	
Comments on the ACD:	
The document states ponesimoids effect on disability is unclear. I totally disagree with this statement. This medication has had a massive effect on my disability, as my disability has not deteriorated at all in the 10 years that I have been taking this medication. Also I have had no relapses in this time either. I feel this medication has had a positive effect on my health and would benefit many other patients with M.S. It seems such a shame that other M.S sufferers will not have the opportunity to benefit from this drug.	

Ponesimod for Relapsing Multiple Sclerosis [ID1393]:

ERG Review of Company's Response to ACD

November 2021

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This document is linked to ERG report	Farmer, O'Toole, Packman, Brand, Robinson, Kiff, Ciccarelli, Counsell, Crathorne, Melendez-Torres. Ponesimod for Relapsing Multiple Sclerosis [ID1393]: A Single Technology Appraisal. Peninsula Technology Assessment Group (PenTAG), 2021.
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1. SUMMARY

In their appraisal consultation document (ACD), the committee raised a number of concerns regarding the clinical and economic evidence presented by the company for ponesimod in the treatment of active and highly active relapsing and remitting multiple sclerosis (RRMS). In this document, the evidence review group (ERG) review additional evidence provided by the company to address these concerns, in advance of a second committee meeting. It should be noted that due to the substantial time constraints posed by the timing of the receipt of evidence against the second committee meeting, the ERG has sought to address key issues only in respect of the evidence presented.

2. ERG APPRAISAL OF THE UPDATED EVIDENCE

In the ACD, the NICE committee noted that the most likely cost-effectiveness estimates for ponesimod are above what NICE normally considers to be an acceptable use of NHS resources. This was due to a high level of uncertainty around the incremental cost-effectiveness ratios (ICERs). In particular, the committee noted uncertainty in the following:

- The results from the network meta-analyses (NMAs), and including interferons as a single class in the network [ACD section 3.7 and 3.10]
- Limitations in the model structure [ACD section 3.12]
- Credibility of the modelled output [ACD section 3.13]
- Updated evidence on mortality [ACD section 3.14]

In this section, the ERG appraise additional evidence presented by the company to address these uncertainties.

2.1. Uncertainty surrounding the company's NMAs

The committee noted limitations in the company's NMAs highlighted by the ERG, including extreme heterogeneity of trial designs, short-term effects, and wide credible intervals around the effect estimates.

At technical engagement the company attempted to address heterogeneity amongst trials of interferon treatments, which are a key comparator for ponesimod in the active RRMS population, by pooling interferon treatments. In the ACD, the committee noted that a hierarchical class-based model may be preferable than simply pooling interferons in the analysis. Moreover, it suggested that it would be helpful to include trials of interferons excluded from the company's analyses, though acknowledged that these would not contribute to estimates of treatment effect. Consistency and model fit indices for these analyses were also requested by the committee.

2.1.1. Hierarchical class-based approach to interferon treatments

The ERG considered the methods used in this hierarchical class-based NMA for interferon regimens to be broadly appropriate; it noted, however, that it was not possible to appraise the specific approaches used, as outputs from the company analyses were not accessible and time precluded the reproduction of the analyses. Broadly speaking, results were very similar across approaches, though a model considering the interferons as a class was slightly more

favourable to ponesimod against some treatments for clinical outcomes (though this effect was less consistent for treatment discontinuation). The results of the class-based hierarchical model more closely resembled those from the model considering the interferons as separate treatments, though results from the former were more imprecise with wider 95% credible intervals (CrIs) around the effect estimates. The ERG also noted that the class-based hierarchical model did not present interferon-specific estimates.

The ERG considered the trial exclusions in updated iterations of the NMA to be broadly appropriate and consistent with previous approaches. For the model considering interferons as a class, the EVIDENCE trial(1) was excluded for all outcomes of interest as it only evaluated interferons; the trial by Mokhber et al. 2015(2) and the REFORMS trial(3) were similarly excluded from this model for treatment discontinuations, for the same reason. The ADVANCE trial(4) was additionally excluded from the class-based hierarchical model for all outcomes of interest as it is described as an outlier with clinically implausible results. Results from the INCOMIN study(5) were also excluded as outliers from the class-based hierarchical model for annualised relapse rate (ARR) and treatment discontinuations. The ERG noted that these exclusions are consistent with the approach in the recent appraisal of ofatumumab (TA699). The INCOMIN study(5) did not provide data for confirmed disability accumulation (CDA) at 3 months and did not report CDA at 6 months as a hazard ratio (HR), and therefore could not be included in these analyses.

The results of the hierarchical class-based NMA for ARR are presented in Table 1, along with the results of previous NMAs considering interferons as a class (presented in appraisal committee meeting 1) and as separate treatments (as presented in the company's original submission). The results from the various approaches were similar across the majority of treatments, with rate ratios (RRs) differing by 0.1 or less. However, as compared to the hierarchical model or the model treating interferons as individual treatments, analyses using interferons as a class resulted in lower RRs for ponesimod as compared to ocrelizumab and alemtuzumab (i.e. more favourable for ponesimod). None of the results across treatment comparisons differed by 0.2 or more between RRs using different approaches.

Table 1 NMA results for ARR, considering interferon regimens in a class-based hierarchical model, as a class or as separate treatments comparing treatments with ponesimod

Comparator intervention [a]	Class-based hierarchical model (fixed effect); RR (95% CrI) [excluding ADVANCE(4) and INCOMIN(5)]	Model considering interferons as a class (fixed effect); RR (95% CrI) [excluding EVIDENCE(1)]	Model considering interferons as separate treatments (fixed effect); RR (95% CrI)

OFA 20 4W	[redacted]	[redacted]	[redacted]
OCR 600 24W	[redacted]	[redacted]	[redacted]
ALE 12 QD	[redacted]	[redacted]	[redacted]
NAT 300 4W	[redacted]	[redacted]	[redacted]
FIN 0.5 QD	[redacted]	[redacted]	[redacted]
OZA 1 QD	[redacted]	[redacted]	[redacted]
DMF 240 BID	[redacted]	[redacted]	[redacted]
CLA 3.5 mg/kg QD	[redacted]	[redacted]	[redacted]
TER 14 QD	[redacted]	[redacted]	[redacted]
GA 20 QD	[redacted]	[redacted]	[redacted]
GA 40 TIW	[redacted]	[redacted]	[redacted]
IFN class	[redacted]	[redacted]	[redacted]
IFNB-1a 22 µg SC TIW	[redacted]	[redacted]	[redacted]
IFNB-1a 30 µg IM QW	[redacted]	[redacted]	[redacted]
IFNB-1a 44 µg SC TIW	[redacted]	[redacted]	[redacted]
IFNB-1b 250 µg QOD	[redacted]	[redacted]	[redacted]
PEG 125 µg 2W	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]

Abbreviations: ALE, alemtuzumab 12 mg once daily; CLA, cladribine 3.5 mg/kg once daily; CrI, credible interval; DMF, dimethyl fumarate 240 mg twice daily; FIN, fingolimod 0.5 mg once daily; GA 20, glatiramer acetate 20 mg once daily; GA 40, glatiramer acetate 40 mg three times weekly; IFN, interferon; IFNB-1a 22 µg, interferon beta-1a 22 µg subcutaneously three times weekly; IFNB-1a 30 µg , interferon beta-1a 30 µg intramuscular once weekly; IFNB-1a 44 µg , interferon beta-1a 44 µg subcutaneously three times weekly; IFNB-1b 250 µg, interferon beta-1b 250 µg every other day; NA, not applicable; NAT, natalizumab 300 mg every four weeks; OCR, ocrelizumab 600 mg every six months; OFA, ofatumumab 20 mg every four weeks; OZA, ozanimod 1 mg once daily; PBO, placebo; PEG 125 µg, peginterferon beta-1a 125 µg every two weeks; PON, ponesimod 20 mg once daily; RR, rate ratio; TER, teriflunomide 14 mg once daily

Note:

[a] Effect estimates less than 1 indicate that ponesimod is favoured

The results of the different NMAs for confirmed disability accumulation (CDA) at 3 months are presented in Table 2. The results were similar across the majority of treatments, with HRs differing by 0.1 or less. However, as with ARR, the model considering interferons as a class resulted in lower HRs for ocrelizumab and alemtuzumab (i.e. more favourable for ponesimod), compared to the other approaches. Only the results across treatment comparisons for ocrelizumab between interferons as a class and as individual treatments differed by 0.2 or more (difference of 0.21), with the former favouring ponesimod more than the latter.

Table 2 NMA results for 3-month CDA, considering interferon regimens in a class-based hierarchical model, as a class or as separate treatments comparing treatments with ponesimod

Comparator intervention [a]	Class-based hierarchical model (fixed effect); HR (95% CrI) [excluding ADVANCE(4)]	Model considering interferons as a class (fixed effect); HR (95% CrI) [excluding EVIDENCE(1)]	Model considering interferons as separate treatments (fixed effect); HR (95% CrI)
OFA 20 4W	[redacted]	[redacted]	[redacted]
OCR 600 24W	[redacted]	[redacted]	[redacted]
ALE 12 QD	[redacted]	[redacted]	[redacted]
NAT 300 4W	[redacted]	[redacted]	[redacted]
FIN 0.5 QD	[redacted]	[redacted]	[redacted]
OZA 1 QD	[redacted]	[redacted]	[redacted]
DMF 240 BID	[redacted]	[redacted]	[redacted]
CLA 3.5 mg/kg QD	[redacted]	[redacted]	[redacted]
TER 14 QD	[redacted]	[redacted]	[redacted]
GA 20 QD	[redacted]	[redacted]	[redacted]
IFN class	[redacted]	[redacted]	[redacted]
IFNB-1a 22 µg SC TIW	[redacted]	[redacted]	[redacted]
IFNB-1a 30 µg IM QW	[redacted]	[redacted]	[redacted]
IFNB-1a 44 µg SC TIW	[redacted]	[redacted]	[redacted]
PEG 125 µg 2W	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]

Abbreviations: ALE, alemtuzumab 12 mg once daily; CLA, cladribine 3.5 mg/kg once daily; CrI, credible interval; DMF, dimethyl fumarate 240 mg twice daily; FIN, fingolimod 0.5 mg once daily; GA 20, glatiramer acetate 20 mg once daily; HR, hazard ratio; IFN, interferon; IFNB-1a 22 µg, interferon beta-1a 22 µg subcutaneously three times weekly; IFNB-1a 30 µg , interferon beta-1a 30 µg intramuscular once weekly; IFNB-1a 44 µg , interferon beta-1a 44 µg subcutaneously three times weekly; NA, not applicable; NAT, natalizumab 300 mg every four weeks; OCR, ocrelizumab 600 mg every six months; OFA, ofatumumab 20 mg every four weeks; OZA, ozanimod 1 mg once daily; PBO, placebo; PEG 125 µg, peginterferon beta-1a 125 µg every two weeks; PON, ponesimod 20 mg once daily; TER, teriflunomide 14 mg once daily

Note:

[a] Effect estimates less than 1 indicate that ponesimod is favoured

The results of the hierarchical class-based NMA, along with the results of previous NMAs considering interferons as a class and as separate treatments, for CDA at 6 months are presented in Table 3. Various approaches yielded similar results across the majority of treatments, with HRs differing by 0.1 or less; the exception being effects when considering the interferons as a class versus considering these as separate treatment, or in a class-based hierarchical model, for ocrelizumab and alemtuzumab. Analyses using interferons as a class resulted in lower HRs for ocrelizumab and alemtuzumab (more favourable for ponesimod).

None of the results across treatment comparisons differed by 0.2 or more between HRs using different approaches.

Table 3 NMA results for 6-month CDA, considering interferon regimens in a class-based hierarchical model, as a class or as separate treatments comparing treatments with ponesimod

Comparator intervention [a]	Class-based hierarchical model (fixed effect); HR (95% CrI) [excluding ADVANCE(4)]	Model considering interferons as a class (fixed effect); HR (95% CrI) [excluding EVIDENCE(1)]	Model considering interferons as separate treatments (fixed effect); HR (95% CrI)
OFA 20 4W	[redacted]	[redacted]	[redacted]
OCR 600 24W	[redacted]	[redacted]	[redacted]
ALE 12 QD	[redacted]	[redacted]	[redacted]
NAT 300 4W	[redacted]	[redacted]	[redacted]
FIN 0.5 QD	[redacted]	[redacted]	[redacted]
OZA 1 QD	[redacted]	[redacted]	[redacted]
DMF 240 BID	[redacted]	[redacted]	[redacted]
CLA 3.5 mg/kg QD	[redacted]	[redacted]	[redacted]
TER 14 QD	[redacted]	[redacted]	[redacted]
GA 20 QD	[redacted]	[redacted]	[redacted]
IFN class	[redacted]	[redacted]	[redacted]
IFNB-1a 30 µg IM QW	[redacted]	[redacted]	[redacted]
IFNB-1a 44 µg SC TIW	[redacted]	[redacted]	[redacted]
PEG 125 µg 2W	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]

Abbreviations: ALE, alemtuzumab 12 mg once daily; CLA, cladribine 3.5 mg/kg once daily; CrI, credible interval; DMF, dimethyl fumarate 240 mg twice daily; FIN, fingolimod 0.5 mg once daily; GA 20, glatiramer acetate 20 mg once daily; HR, hazard ratio; IFN, interferon; IFNB-1a 30 µg , interferon beta-1a 30 µg intramuscular once weekly; IFNB-1a 44 µg , interferon beta-1a 44 µg subcutaneously three times weekly; NA, not applicable; NAT, natalizumab 300 mg every four weeks; OCR, ocrelizumab 600 mg every six months; OFA, ofatumumab 20 mg every four weeks; OZA, ozanimod 1 mg once daily; PBO, placebo; PEG 125 µg, peginterferon beta-1a 125 µg every two weeks; PON, ponesimod 20 mg once daily; TER, teriflunomide 14 mg once daily

Note:

[a] Effect estimates less than 1 indicate that ponesimod is favoured

The comparative results for treatment discontinuations are presented in Table 4. Treatment discontinuations resulting from the various modelling approaches were similar across some treatments, with odds ratios (ORs) differing by 0.1 or less. Exceptions to this were for ocrelizumab, alemtuzumab, fingolimod, ozanimod and glatiramer acetate at a dosage of 20 mg once daily (GA 20 QD). Analyses using interferons as a class resulted in lower ORs for fingolimod, ozanimod and GA 20 QD (i.e. more favourable for ponesimod), and higher ORs for

ocrelizumab, and alemtuzumab (i.e. less favourable for ponesimod). In addition, analyses considering interferons in a class-based hierarchical model resulted in higher ORs for ocrelizumab and alemtuzumab when compared to analyses considering interferons as separate treatments. The differences for ocrelizumab, alemtuzumab and GA 20 QD exceeded 0.2 when comparing the interferons as a class versus considering these as separate treatments; these were large for ocrelizumab (difference of 0.44) and very large for alemtuzumab (difference of 1.22).

Table 4 NMA results for treatment discontinuations, considering interferon regimens in a class-based hierarchical model, as a class or as separate treatments comparing treatments with ponesimod

Comparator intervention [a]	Class-based hierarchical model (random effects with vague priors); OR (95% CrI) [excluding ADVANCE(4) and INCOMIN(5)]	Model considering interferons as a class (random effects with vague priors); OR (95% CrI) [excluding EVIDENCE(1), Mokhber et al. 2015(2) and REFORMS(3)]	Model considering interferons as separate treatments (random effects with vague priors); OR (95% CrI)
OFA 20 4W	[redacted]	[redacted]	[redacted]
OCR 600 24W	[redacted]	[redacted]	[redacted]
ALE 12 QD	[redacted]	[redacted]	[redacted]
NAT 300 4W	[redacted]	[redacted]	[redacted]
FIN 0.5 QD	[redacted]	[redacted]	[redacted]
OZA 1 QD	[redacted]	[redacted]	[redacted]
DMF 240 BID	[redacted]	[redacted]	[redacted]
CLA 3.5 mg/kg QD	[redacted]	[redacted]	[redacted]
TER 14 QD	[redacted]	[redacted]	[redacted]
GA 20 QD	[redacted]	[redacted]	[redacted]
GA 40 TIW	[redacted]	[redacted]	[redacted]
IFN class	[redacted]	[redacted]	[redacted]
IFNB-1a 22 µg SC TIW	[redacted]	[redacted]	[redacted]
IFNB-1a 30 µg IM QW	[redacted]	[redacted]	[redacted]
IFNB-1a 44 µg SC TIW	[redacted]	[redacted]	[redacted]
IFNB-1b 250 µg QOD	[redacted]	[redacted]	[redacted]
PEG 125 µg 2W	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]

Abbreviations: ALE, alemtuzumab 12 mg once daily; CLA, cladribine 3.5 mg/kg once daily; CrI, credible interval; DMF, dimethyl fumarate 240 mg twice daily; FIN, fingolimod 0.5 mg once daily; GA 20, glatiramer acetate 20 mg once daily; GA 40, glatiramer acetate 40 mg three times weekly; IFN, interferon; IFNB-1a 22 µg, interferon beta-1a 22 µg subcutaneously three times weekly; IFNB-1a 30 µg , interferon beta-1a 30 µg intramuscular once weekly; IFNB-1a 44 µg , interferon beta-1a 44 µg subcutaneously three times weekly; IFNB-1b 250 µg,

interferon beta-1b 250 µg every other day; NA, not applicable; NAT, natalizumab 300 mg every four weeks; OCR, ocrelizumab 600 mg every six months; OFA, ofatumumab 20 mg every four weeks; OR, odds ratio; OZA, ozanimod 1 mg once daily; PBO, placebo; PEG 125 µg, peginterferon beta-1a 125 µg every two weeks; PON, ponesimod 20 mg once daily; TER, teriflunomide 14 mg once daily

Note:

[a] Effect estimates less than 1 indicate that ponesimod is favoured

In conclusion, the updated NMA considering interferon regimens in a class-based hierarchical model resulted in very similar effect estimates as previous models, and most resembled the approach considering the interferons as separate treatments, though effect estimates were less precise. The ERG noted that the model considering the interferons as a class appeared to favour ponesimod more than those using a class-based hierarchical approach or considering interferon regimens as separate treatments. The ERG did not consider the results from the class-based hierarchical model to change its previous conclusions around the clinical effectiveness of ponesimod.

2.1.2. NMA model fit and analysis of inconsistency

The company used a global approach to evaluating inconsistency in the network by comparing 'consistent' and 'inconsistent' (i.e. unrelated mean effects) base case models for ARR, CDA-3, CDA-6, and all-cause treatment discontinuations. The company presented model fit indices (deviance information criterion [DIC], total residual deviance, and 'SD', which we assume to be the between-study standard deviation) for (a) the NMA in the active RRMS population presented at the first committee meeting (i.e. where interferons were pooled) and (b) the hierarchical class-based NMA presented in their response to ACD (see Section 2.1.1). In addition, for the class-based NMA the posterior mean deviance for all outcomes was plotted for the class-based NMA. The company stated that their approach was consistent with methods described in NICE technical support document 4 (TSD4).(6) The company did not report local measures of inconsistency (i.e. a comparison of direct and indirect evidence for specific comparisons). On the basis of the results, the company considered that the two models were comparable, and therefore they concluded that the NMAs showed good consistency.

In general, it is recommended that researchers use both local and global approaches to evaluating inconsistency, and report both sets of results (Cochrane manual, Chapter 11).(7) This is because it is challenging difficult to detect inconsistency in NMAs, and simple tests lack statistical power for detecting differences in direct and indirect evidence. This problem is exacerbated for NMAs with a high degree of heterogeneity (as in this case), as while heterogeneity increases the risk of uncertainty, it also decreases the chance that inconsistency will be detected. Thus, evaluating the presence of inconsistency requires a

broad approach, including consideration of likely sources of heterogeneity in effect modifiers across trials. In general, advice in NICE TSD4 is that researchers are rarely able to reject the null hypothesis for consistency, and should not conclude that any analysis shows good consistency.(6)

On the basis of the new evidence supplied by the company, the ERG does not consider that the null hypothesis for consistency can be rejected. As discussed previously in the appraisal of ponesimod, it is widely accepted that NMAs of treatments for RRMS are highly heterogeneous, with varying trial populations and designs. This does not necessarily lead that relative treatment effects will be significantly affected, however the ERG considers this to be a significant risk for this appraisal, and therefore the treatment effects for ponesimod (and all other treatments in the network) are considered to be uncertain. Clinical experts in the NICE committee meeting noted that the results of the NMAs are generally consistent with clinical practice, although the ERG notes that even small variation in treatment effects have been shown to meaningfully impact the ICER.

As acknowledged previously by the ERG, the company have conducted these analyses based on the best available evidence, and in accordance with previous NMAs for treatments appraised by NICE. Until such time as there is evidence that relative treatment effects are unaffected by distributions of effect modifiers across the network, or it is possible to conduct meta-regression analyses on a meaningful subset of the trials (as this has been shown to not be feasible in the current evidence base), a degree of uncertainty will remain surrounding the clinical effects of treatment.

2.2. Limitations in the company's model structure

The committee acknowledged that the model structure presented by the company was consistent with the models accepted in previous NICE appraisals of treatments for RRMS; however, it considered that the model structure has limitations. Clinical experts advised that several of the assumptions in the model may not accurately represent current understanding of the natural history of multiple sclerosis, factors affecting treatment efficacy, the long-term efficacy of treatment, or the current treatment pathway. The committee noted that previous appraisals had critiqued the lack of treatment switching or sequencing and the fixed treatment waning effect as major limitations of similar models. It considered that these oversimplify what would happen in NHS clinical practice.

The committee acknowledged that there is limited data to support an alteration of some assumptions in the company's model, and that alternative model structures may be complex

to construct and difficult to populate. The company did not submit an alternative model structure in their response, and this remains an outstanding area of uncertainty.

2.3. Credibility of the modelled output

As noted in section 3.13 of the ACD, the committee noted that "*the modelled outputs, including total quality adjusted life year (QALY) gain, from the economic model were inconsistent with other appraisals".* The company noted that outputs for beta interferons and glatiramer acetate (TA527) were unusually high, however stated it was not possible to determine why given that model input details were not available in TA527. The ERG understood that QALYs were relatively high in TA527 because the preferred base case incorporated risk sharing scheme data, which were compared against the natural history without any matching or adjustment. As such, TA527 represents an outlier with respect to QALY outputs when compared to other MS appraisals.

To address NICE's concern surrounding modelled total QALYs, the company validated their model outputs using peginterferon (TA624) model inputs in their ponesimod model. The ERG noted that the company were not able to utilise all peginterferon model inputs; i.e. the treatment effects were based on the company NMAs which were redacted. As shown in Table 5 below, total QALYs for treatment comparators were broadly similar to the company's original model, demonstrating that the company's model is likely to be reasonable. Overall, the ERG considered that the company's model is adequate for decision making and noted that the reason outputs vary with respect to QALY gain (compared to previous MS appraisals) is due to the differences in model inputs such as treatment effect estimates and baseline characteristics.

Similarly, with respect to time spent in SPMS, the company compared the average time spent in SPMS (estimated in their model) to the time spent in SPMS (estimated in peginterferon TA624). The ERG noted that average time spent in SPMS was slightly higher in the ponesimod model ([redacted]) than peginterferon TA624 (65%), however outputs appeared broadly in line. As an additional measure of validity, the company further used peginterferon TA624 model inputs in the ponesimod model to determine whether time spent in SPMS is aligned. Based on this approach, both models produced similar SPMS time outputs, with minimal difference between comparators (see Table 6).

Table 5: Comparison of QALYs between ponesimod and peginterferon (TA624)

Treatment	QALYs (Janssen model)	QALYs (peginterferon model inputs)	Difference
Teriflunomide	[redacted]	[redacted]	[redacted]
DMF	[redacted]	[redacted]	[redacted]
GA 20	[redacted]	[redacted]	[redacted]

Treatment	QALYs (Janssen model)	QALYs (peginterferon model inputs)	Difference
Ocrelizumab	[redacted]	[redacted]	[redacted]

Abbreviations: DMF, dimethyl fumarate; GA, glatirimer acetate; QALY, quality-adjusted life year

Table 6: Time spent in SPMS stated in ponesimod and peginterferon model

Treatment	% Time spent in SPMS % (Janssen base case analysis a) %	Time spent in SPMS (Janssen model with Peg inputs b)	% Time spent in SPMS (peginterferon model c)	Difference (model b – model c)
Teriflunomide	[redacted]	[redacted]	[redacted]	[redacted]
Dimethyl Fumarate	[redacted]	[redacted]	[redacted]	[redacted]
Glatiramer Acetate	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]

Source: Company response to ACD

Abbreviations: SPMS, secondary progression multiple sclerosis

2.4. Updated evidence on mortality

As noted in the ACD, NICE considered the source for mortality (Pokorski et al.)(8) to be outdated, and that they expected the management of acute infection and nursing has reduced mortality in patients with MS. As such the committee considered that a scenario analysis using a more recent data source would be helpful to explore uncertainty and the impact on cost effectiveness results.

The paper by Pokorski et al.(8) has notable limitations and the ERG agree with NICE's assessment that it is an outdated source. The paper, published in 1997, was based on patient data from the Danish MS registry. This was an epidemiological survey that included 'virtually' everyone diagnosed with definite, probable or possible MS in Denmark since 1948. However, the mortality data used in the company's original economic model was based on mortality from a Canadian study reported in a single table at the end of the Pokorski et al. paper. Patient characteristics were not provided for the 2348 patients in this cohort, study methodology was not outlined, and mortality was not provided according to EDSS health state, but rather according to disease severity (mild, moderate and severe).

In their revised base case analysis, the company used a relatively recent UK study by Harding et al. (2018)(9) to estimate alternative mortality estimates for EDSS health states in the model. The company used mortality rates from Harding et al. for modelled EDSS states 4-9, however they used rates from Pokorski et al.(8) for EDSS states 0-3. This was because mortality rates were not reported for EDSS states 0-3 in Harding et al. Modelled risks of mortality used in the company model are reported in Table 7.

Mortality rates were higher in Harding et al. compared to Pokorski et al., which means that the company's revised model resulted in fewer life years compared to its original model. This was contrary to expectation, as the ERG had anticipated improved mortality for these patients, given the more recent nature of Harding et al. and advances in MS treatment since the Pokorski et al. cohort. The ERG noted, however, that Harding et al. states that disease modifying treatment (DMT) had only been widely available in Wales since 2002, and that a minority of patients in the study had been treated with DMT (38% of those diagnosed since 2002, and 11.7% of those diagnosed before 2002). The authors state that these data therefore represent a natural history cohort of 'untreated' patients. Additionally, the estimation of mortality risk by EDSS score in Harding et al. was based on relatively few patient deaths, which may limit the robustness of these results; i.e. there were 9, 16 and 29 deaths recorded in EDSS states 4-5.5, 6-6.5 and 7-7.5 respectively.

The ERG considered that despite the limitations surrounding Harding et al.(9), this study may be a more appropriate source for use in the model, given that it is more generalisable to the UK, and included a reasonably large cohort of patients (n=2604) from the Southeast Wales MS registry. However, due to the lack of granular information presented in the Pokorski et al.(8) paper, the reason for the disparity in mortality estimates between these papers is unclear and time constraints precluded seeking additional clinical opinion. The committee should be aware that due to time constraints, the ERG were unable to conduct a comprehensive literature search to identify alternative plausible mortality sources.

Table 7: Modelled relative risk of mortality (Harding et al.(9), EDSS 4-9; Pokorski et al.(8), EDSS 1-3)

EDSS state	Relative risk
EDSS 0	1
EDSS 1	1.3
EDSS 2	1.60
EDSS 3	1.68
EDSS 4	2.02
EDSS 5	2.02
EDSS 6	3.86

EDSS state	Relative risk
EDSS 7	4.76
EDSS 8	22.17
EDSS 9	60.74

3. COMPANY'S REVISED MODEL FOLLOWING ACD

The company made several changes to their economic model for both the active RRMS and highly active RRMS populations to address areas of outstanding uncertainty identified by NICE in section 3.17 of the ACD. A full list of model revisions are provided in Table 8, alongside ERG commentary regarding the appropriateness of the company's revisions.

Table 8: List of model revisions post ACD 1

Model parameter	Model (presented at ACD 1)	Revised model (post ACD 1)	Committee preferences (from ACD)	ERG commentary on appropriateness of company's revised analysis
NMA inputs	Based on the pooled class-based interferon NMA	Hierarchical class-based interferon NMA	NICE requested the company provide a hierarchical based model for interferons in section 3.17 of the ACD.	Overall, the ERG considered the use of a hierarchical based model for interferons to be appropriate. The ERG noted that there is minimal difference in modelled results when either a hierarchical NMA approach is taken or a pooled class based NMA
Mortality	Pokorski, 1997(8)	Harding et al 2018(9) (with Pokorski, 1997 data for EDSS states 0 – 3)	NICE requested an additional analysis using an alternative source for mortality.	The ERG considered Harding et al. to be a more appropriate source for mortality estimates than Pokorski et al., given that the study is more generalisable to UK patients and is more recent. However, as noted in Section 2.4, there are limitations surrounding Harding et al.
Annual conversion probability from RRMS to SPMS	Mauskopf, et al., 2016(10)	Peginterferon (TA624)	It is unclear whether peginterferon (TA624) reflects NICE's preference.	The ERG considered that deriving conversion probabilities (RRMS to SPMS) from peginterferon (TA624) was appropriate, as these data have been previously used an accepted by NICE.
Transition probability matrices	The company's model used hazard ratios. The ERG made a switch upon Committee lead team request	Revised model uses relative risks	NICE preferred the use of relative risks.	The ERG considered the use of relative risks to be appropriate.

Model parameter	Model (presented at ACD 1)	Revised model (post ACD 1)	Committee preferences (from ACD)	ERG commentary on appropriateness of company's revised analysis
	prior to the committee meeting to convert hazard ratios to relative risks			

3.1. ERG model fixes

The ERG identified several errors in the company's revised model. These are as follows;

- The company used CDA at 3 months in their revised base case. The ERG and NICE committee considered that 6 month CDA was more appropriate, therefore the ERG has re-estimated the company's base case using CDA-6 month results.

- The ERG noted that in the company's revised model (using the hierarchical class-based NMA with updated mortality) the acquisition costs were zero for some of the treatments when 'PAS option' was selected in the ERG settings sheet. Subsequently, ERG identified this was due to an error in the 'Literature data' sheet (AE231:AG250) as when PAS option is selected the formula refers to column AE which was empty. This error has been fixed in the ERG version of the model.

4. COMPANY'S REVISED BASE CASE RESULTS

The company's revised base case results for the active RRMS and highly active RRMS populations are outlined in Table 9 and Table 10. These revised base case results account for the following:

- The company's list of model revisions as per Table 8.
- The appropriate ponesimod PAS discount of [redacted] The ERG noted that the company's revised base case results used a [redacted] discount.
- The ERG model fixes outlined in Section 3.1.

Table 9: Company revised base case results (Active RRMS)

	Discounted costs	Discounted QALYs	Incremental discounted costs	Incremental discounted QALYs	ICER
Ponesimod 20mg PO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Teriflunomide 14mg PO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dimethyl fumarate 240mg PO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glatiramer acetate 20mg SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Interferon class	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab 600mg IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ofatumumab 20mg SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ozanimod 1.0mg PO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life-year

Table 10: Company revised base case results (Highly active RRMS)

	Discounted costs	Discounted QALYs	Incremental discounted costs	Incremental discounted QALYs	ICER
Ponesimod 20mg PO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab 600mg IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ofatumumab 20mg SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ozanimod 1.0mg PO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alemtuzumab 12mg IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cladribine 3.5mg/kg PO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fingolimod 0.5mg PO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life-year

The company provided probabilistic sensitivity analysis (PSA) results for both populations, however the ERG noted that these results included the incorrect PAS of [redacted] and the model errors identified by the ERG. Due to time constraints and the computationally intensive nature of the PSA, the ERG have conducted PSA (run for 3000 simulations) only as part of the cPAS analysis. The ERG consider these results most relevant for decision making.

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