NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Siponimod for treating secondary progressive multiple sclerosis [ID1304]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Siponimod for treating secondary progressive multiple sclerosis [ID1304]

Contents:

The following documents are made available to consultees and commentators:

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

2. **Comments on the Appraisal Consultation Document from Novartis**
   - **Company consultation response**
   - **Company consultation response appendix**

3. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   a. Multiple Sclerosis Society
   b. Multiple Sclerosis Trust
   c. Association of British Neurologists
   d. UK Multiple Sclerosis Specialist Nurse Association

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

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

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

Appraisal title

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	Consultee (company)	Novartis	Novartis is disappointed by the draft recommendation from NICE not to recommend siponimod for the treatment of secondary progressive multiple sclerosis (SPMS) with active disease, especially considering NICE has recognised that treatment options for people diagnosed with SPMS with active disease are extremely limited and that "*siponimod is a promising drug that has the potential to address this unmet clinical need*."[1] Novartis is pleased that the clinical effectiveness and innovation of siponimod has been recognised by NICE, however if the initial decision remains unchanged, patients will be denied access to the first licensed oral therapy for patients with SPMS with active disease, leaving them without an effective, convenient treatment to manage their condition and help them maintain independence for longer. Novartis is grateful for the opportunity to respond to the Appraisal Consultation Document (ACD) to address the outstanding questions and would like to provide further comment and clarification on the remaining uncertainties in the appraisal. In addition to the comments provided here, a revised economic model and supporting Appendix have been provided with NICE's permission with a revised base case, taking into account the committee's preferences: • Fully incremental cost-effectiveness results, comparing siponimod with both interferon β-1b and best supportive care (BSC) • Additional cost for MRI scan for people starting siponimod • Active SPMS utilities as opposed to intention-to-treat (ITT) population utilities • Treatment discontinuation as opposed to study discontinuation • Treatment waning of 50% from Year 11 (in line with the assumptions used in NICE appraisal TA527)[2] • Scenario analyses: inclusion of an extra (3rd) neurology appointment in Year 1; Active SPMS NMA; treatment waning of 25% from Year 7, 50% from Year 10 (in line with available long-term EXPAND data); Active SPMS NMA plus treatment waning of 25% from Year 7, 50% from Year 10; weighted analyses assuming [redacted] of patients receive disease-modifying therapies (DMTs) and [redacted] receive BSC.	Thank you for providing these additional analyses to account for the committee's preferences. The FAD has been amended to reflect that these analyses were considered by the

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 all scenarios of the cost-effectiveness analyses presented in the supporting appendix, including considering BSC as comparator and with the inclusion of treatment waning, [redacted]. [redacted] The following topics are addressed within this response: • The choice of BSC as comparator • Innovation • Treatment administration costs applied in the economic model • Indirect treatment comparisons • Treatment discontinuation rates • Utility values in the economic model • Efficacy in subgroups	committee.
2	Consultee (company)	Novartis	**Due to a hesitancy by clinicians to formally diagnose SPMS, many patients who would be eligible for siponimod are still diagnosed and treated as having relapsing-remitting multiple sclerosis (RRMS)** Section 3.1 of the ACD states that *"the clinical experts, patient experts, company and ERG all indicated that there is a period of transition in which people with relapsing–remitting multiple sclerosis may be suspected of having secondary progressive disease but are not formally diagnosed. This is especially the case for the population of interest in this appraisal, people with active secondary progressive disease, because they may still have relapses*." "*The patient and clinical experts also acknowledged that historically, there has been reluctance to diagnose patients with secondary progressive multiple sclerosis because there is only 1 licensed treatment, which people may already have taken. Also, disease-modifying treatments for relapsing–remitting multiple sclerosis are no longer indicated once someone is diagnosed with secondary progressive multiple sclerosis, so treatment usually stops*." The clinical expert also stated (Section 3.3 of the ACD) that "*disease-modifying therapies are sometimes used outside of their licensed indications in people with secondary progressive multiple sclerosis during the transition period from relapsing–remitting disease*." Additionally, the NHS commissioning expert statement states that *"it is thought that a proportion of patients who may be eligible for siponimod are likely to*	Thank you for your comment. The choice of comparators was considered by

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
			still be receiving treatment with a disease modifying treatment (DMT); this is because distinguishing between relapsing-remitting and progressive phenotypes of MS can be challenging, which, coupled with the lack of active treatments for SPMS, may result in patients remaining on DMTs as their disability progresses (transitioning from RRMS to SPMS)." Given the uncertainty and hesitancy around diagnosing patients as having SPMS, many patients who would be eligible for treatment with siponimod are likely to still be formally diagnosed as having RRMS and therefore still receive their RRMS DMT. As acknowledged by NICE, for patients with active SPMS, the likelihood of being on treatment is much higher than in patients with non-active SPMS: A long-running multiple sclerosis (MS) real world evidence study in the UK showed that, in Q4 2019, [redacted] of sampled active SPMS patients were currently receiving treatment, compared with [redacted] of sampled patients with non-active SPMS.[3] Although NHS England does not commission DMTs (other than Extavia®) for patients with active SPMS, as identified by both the clinical and commissioning experts, DMTs are used in clinical practice in the undiagnosed population of patients with active SPMS. Therefore, the most appropriate comparator for siponimod should be DMTs used outside their licensed indications, as listed in the NICE scope. Novartis acknowledges that there will be a mix of patients (some currently treated whilst others are not) who would receive siponimod treatment. In order to explore this, a scenario analysis is presented in the supporting Appendix considering a weighted incremental cost-effectiveness ratio (ICER) for the analyses versus BSC and Extavia®, using the assumption that [redacted] of patients with active SPMS are receiving a DMT. This analysis conservatively assumes that all patients receiving DMT are receiving Extavia®, a lower cost DMT. The new base case analysis submitted as part of this response considers BSC as a relevant comparator, in line with the committee's preferences, however in reality, as indicated by NICE, the ERG and the patient and clinical experts, many patients eligible for siponimod are likely to be not currently diagnosed as active SPMS, therefore receiving a DMT, and may be diagnosed as having active SPMS upon siponimod availability.	the committee (see section 3.3 of the FAD). The committee saw the weighted incremental cost-effectiveness ratio (ICER) for the analyses versus best supportive care and Extavia.
3	Consultee (company	Novartis	**Siponimod is an innovative treatment offering cognitive benefits for patients in a phase of MS where there are currently limited to no treatment options** Section 3.16 of the ACD states that "*The ERG agreed that there is some evidence suggesting that siponimod benefits cognitive processing speed and that*	Thank you for your comme

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 EQ-5D may not fully capture this. The committee considered that such benefits could be important but the company had not included them in its model, nor had the company presented it with sufficient evidence of these benefits*." As noted by the committee, cognitive benefits are an important factor in treatment for patients with SPMS. It has been previously documented that cognitive impairment can have a substantial negative impact on the lives of people living with MS, affecting their quality of life, employability and social interactions.[4, 5] Clinical experts have additionally highlighted that cognition is an important part of patients' wellbeing: deterioration in cognition leads to loss of jobs, independence, and self-care ability, and impacts on social relationships, all of which have substantial impacts on mental health.[6-8] Previous studies have observed that cognition is a significant predictor of overall health-related quality of life (including both psychosocial and physical components).[9] Yet, changes in cognitive symptoms are often overlooked and underreported.[4] Cognitive impairment is one of the most disabling aspects of MS, affects 50–70% of all patients with MS and is more severe in patients with SPMS.[10] Therefore, preserving cognitive function constitutes a key aim of disease-modifying MS treatments. The symbol digit modalities test (SDMT) has been suggested as the preferred test for assessing cognitive processing speed by the Multiple Sclerosis Outcome Assessments Consortium which developed its recommendations in collaboration with the Food and Drug Administration (FDA) and European Medicines Agency (EMA).[11] Among the tests of processing speed, SDMT has the strongest relationship with a brain MRI metric that is associated with cognitive performance.[12] Additionally, UK clinicians at a health technology assessment (HTA) advisory board confirmed that the SDMT is a good screening test for cognition in MS. As presented in Section B.2.6.6 of the company submission, scores on the SDMT improved in patients in the siponimod group at Month 12 and 24 in the EXPAND trial (indicating improved cognitive processing speed over time), compared with a worsening of mean scores in the placebo group. Furthermore, the proportion of patients with sustained clinically meaningful improvement (≥4 points from baseline sustained on all subsequent assessments) in SDMT was significantly greater among siponimod- versus placebo-treated patients (HR 1.28; 95% CI: 1.05, 1.55; p=0.0131).[13] The proportion of patients with a sustained clinically meaningful deterioration in SDMT was significantly less in siponimod treated patients versus placebo (HR 0.79; 95% CI: 0.65, 0.96; p=0.0157), equating to a 21% risk reduction in 6-month confirmed deterioration in SDMT of ≥4 points for siponimod compared with placebo.[13] In patients with Active SPMS, siponimod significantly reduced the risk of 6-month confirmed deterioration in SDMT of ≥4 points by 27%.[14] Additional long-term data (up to 5-years) from the open-label extension phase of the EXPAND trial , on the effect of siponimod on SDMT were presented in Section B.1.1. of Appendix B during the technical engagement response. In the open-label extension phase of the EXPAND trial, all patients received siponimod. Over this longer time period, the risk of 6-month confirmed clinically meaningful worsening in cognitive processing speed was reduced by 23% in the continuous siponimod group versus the placebo switching group, demonstrating a maintenance of effect on cognition in the long-term. The time to 6-month confirmed worsening was prolonged by 55%.[15]	nt. The committee considered the evidence on siponimod's effects on cognition (see section 3.14 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 recently published EXPAND data presented at the European Academy of Neurology and the American Academy of Neurology congresses earlier this year, siponimod consistently slowed cortical grey matter and thalamic atrophy. The beneficial effect was consistently observed independent of age, and disease duration, activity and severity.[16] A reduction of grey matter atrophy might positively impact long-term clinical outcomes, including disability progression and cognitive decline.[17-22] The ERG has acknowledged that the EQ-5D may not fully capture any benefits for cognitive processing speed. Cognitive benefits are also not captured in the Expanded Disability Status Scale (EDSS) or relapses within the cost-effectiveness model. As such, the cost-effectiveness results do not account for these additional, important patient benefits; the ICERs presented in this appraisal are therefore an overestimate compared with the true cost-effectiveness of siponimod. Professor Dawn Langdon, a Professor of Neuropsychology at Royal Holloway, University of London, whose work focuses mainly on cognitive aspects of multiple sclerosis, has provided an additional statement on the importance of cognition for patients with MS, which has been provided as an attachment to this response. Beyond cognition, siponimod represents an innovative treatment for patients for whom there are very limited treatment options available. SPMS is a typically hard-to-treat population, as demonstrated by natalizumab, one of the highly efficacious drugs licensed for RRMS, having failed in a trial in patients with SPMS.[23] None of the available DMTs in the UK have been shown to slow disability progression or cognitive impairment in a representative population of patients with SPMS.[24-27] The fact that the committee consider BSC to be the most appropriate comparator for siponimod further highlights the innovative nature of siponimod in providing a treatment to patients who are currently underserved by existing treatment options. Section 3.2 of the ACD states that "*the committee concluded that people may be formally diagnosed with secondary progressive multiple sclerosis earlier if siponimod is available*." This represents a substantial step-change in the transition and management of SPMS in the NHS, directly resulting from the availability of siponimod. Introduction of siponimod would reduce the hesitancy of formally identifying SPMS in patients and would give patients with active SPMS the option to switch to a DMT proven to be efficacious in SPMS. As an oral treatment, siponimod additionally avoids the administration requirements of infusions or injections, whilst also providing greater convenience to patients, allowing them to maintain independence for longer. As noted in the technical report for this appraisal (Section 2.4), Extavia® is "*supplied as a solvent and powder which patients (or carers) must mix in order to take. This may be difficult for people with manual dexterity, visual or cognitive difficulties, which are common in people with multiple sclerosis*." Notably, in the NICE multiple technology appraisal for beta-interferons and glatiramer acetate, the committee concluded that interferon β-1a was a cost-effective use of NHS resources for patients with RRMS, despite ICERs above the typical £30,000 threshold, by taking "*into account the equality considerations applied with respect to the group of people who will find the preparation and administration of Extavia challenging*."[2] Given the importance of benefits in cognitive outcomes for patients, Novartis would appreciate the committee's recognition of the clinically meaningful	

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
			cognitive processing speed data available and innovative nature of siponimod. Siponimod addresses multiple unmet needs for patients with SPMS with active disease: siponimod helps slow declining cognitive function as well as slowing disability progression and reducing relapse rates, and as an oral therapy, offers patients an effective, convenient treatment option that allows patients to maintain their independence for longer.	
4	Consultee (company)	Novartis	**The economic model already captures neurology appointments for patients with active SPMS** Section 3.13 of the ACD states that "*before starting treatment, people being considered for siponimod would attend a neurology clinic and have an MRI scan that they would not normally have been offered. The clinical expert highlighted that these costs would apply only to people who had already been diagnosed with secondary progressive multiple sclerosis, and not to people who are transitioning from relapsing–remitting to secondary progressive disease who would generally have regular MRI scans. The committee concluded that costs associated with additional neurology visits and scans should be included in the model.*" The revised model submitted to NICE as part of this response incorporates the cost of an additional MRI scan for all patients receiving siponimod. This is an overestimate of the true costs to the NHS in clinical practice for two main reasons outlined below: • Firstly, the license wording for siponimod is for "*adult patients with SPMS with active disease evidenced by relapses **or** imaging features of inflammatory activity*." The definition of active SPMS required for initiation of siponimod is not dependent solely on observing imaging features by MRI. In the EXPAND trial, more patients in the Active SPMS subgroup had signs of relapse activity than those with MRI activity: 75.8% of patients had experienced a relapse in the previous 2 years prior to screening, compared with 44.9% of patients with at least one gadolinium (Gd)-enhancing T1 lesion at baseline.[28] The committee concluded in section 3.4 of the ACD that the Active SPMS subgroup from the EXPAND trial is representative of the NHS population of patients with active SPMS. As such, the majority of patients with active SPMS in clinical practice present with clinical features of disease activity through relapses and are eligible for treatment without the requirement for MRI evidence of disease activity. • Secondly, section 3.2 of the ACD states that "*the committee concluded that people may be formally diagnosed with secondary progressive multiple sclerosis earlier if siponimod is available and that diagnosis would involve an MRI scan*." This acknowledged shift to earlier diagnosis for patients with SPMS suggests that many siponimod-eligible patients would be those with RRMS with signs of progression, and therefore are expected to be receiving treatment and care and receiving regular MRI scans. As such, in patients who are already observed to be transitioning to SPMS but for whom, to date, there has been a hesitancy around a formal diagnosis, an additional MRI scan would not be required as this evidence would already have been collected in previous, regular scans. Clinicians would be best placed to determine if an MRI is required or not in order to define disease activity in these patients. The original economic model already includes two neurology appointments associated with siponimod treatment each year, including both a higher cost of a first appointment as well as a follow-up appointment in Year 1.	Thank you for your comment. The committee considered the company's approach to modelling neurology appointments and MRI scans (please see section 3.12 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
			Patients already diagnosed with SPMS, currently receiving BSC, are less likely to have regular appointments. Although the decision to prescribe siponimod may result in a neurologist visit for these patients, this is already accounted for with the two neurologist appointments for all patients in Year 1 of the model. As requested by the committee, a scenario is presented in the supporting Appendix to include an additional (i.e. third) neurology appointment in Year 1, however this is unlikely to be reflective of true clinical practice, and the model already incorporates both first and follow-up appointments in Year 1 independent of the patient's current care (ongoing DMT treatment or BSC). Novartis would be grateful if the committee would re-consider whether the costs of two neurology appointments in Year one (and following years) already included in the model are sufficient, and to recognise that the assumption that an MRI for all patients is conservative, with clinicians being best placed to determine its appropriateness.	
5	Consultee (company)	Novartis	**The European Study Group (EU) study matching-adjusted indirect comparison (MAIC) results in a less robust and more uncertain comparison than the North American study MAIC** Section 3.8 of the ACD states that "*in the trial of interferon beta-1b by the European Study Group, known as the European trial, about 70% of people had relapses, indicating probable active disease. It considered that a matching-adjusted indirect comparison using only this trial data may provide a more reliable result than any of the indirect comparisons it had been presented with so far." "Given the uncertainties in the indirect comparisons, it would be valuable to see a matching-adjusted indirect comparison using data from the European trial.*" In the company submission, a MAIC for 3-month confirmed disability progression (CDP) was presented for the EU Study (6-month CDP data are not available from the EU Study), 6-month CDP for the North American Study, and for annualised relapse rate (ARR) a matched comparison to the average baseline characteristics of the EU and North American Studies (Section B.9.2.4 of Document B; results in Tables 41 and 42, pages 76 and 77, respectively). Novartis notes that NICE acknowledges the MAIC as an appropriate indirect treatment comparison method for this appraisal. However, although the EU study has a larger proportion of relapsing patients than the North American study, there are a number of concerns that are raised when considering the EU study for comparing treatment efficacy between siponimod and interferon β-1b which are outlined below: • The EU study population is considerably younger than both the North American and EXPAND trial populations: mean age of 41.0 years in EU study; 46.8 years in North American study; 48.0 years in the EXPAND ITT; and 46.6 years in the EXPAND Active SPMS subgroup.[28-31] Section 3.4 of the ACD states that "*the committee concluded that the baseline characteristics of the active disease subgroup in EXPAND are similar to the NHS population with active secondary progressive multiple sclerosis*." Therefore, it is questionable whether a younger population such as that seen in the EU study is reflective of the UK active SPMS population. Additionally, clinical experts at HTA advisory boards ranked age as the most influential treatment effect modifier for CDP when considering indirect treatment comparisons.	Thank you for your comment. The committee was made aware of your concerns relating to the EU study MAIC and considered the choice of indirect comparison. Please see

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
			• As stated, MAICs to both the EU and North American studies were presented in the company submission. However, in the comparison to the EU study, the effective sample size (N_{eff}) following matching and adjustment is reduced to less than 10% of the EXPAND ITT for 3-month CDP; N_{eff} was [redacted] for the EU study (3-month CDP), compared with [redacted] when using the North American study (6-month CDP). As noted by the ERG (section 3.7 of the ACD), reduced sample sizes increase the uncertainty. This substantial difference in N_{eff} means the results of the comparison with the EU study are much less robust and are subject to greater uncertainty than the results of the NA study comparison. • Additionally, 6-month CDP data are not available from the EU study. 6-month CDP is a more specific outcome measure for disability progression than 3-month CDP. Confirmation of progression at 3-months may be biased by incomplete relapse recovery. NICE has consistently favoured the use of 6-month CDP as a more appropriate measure of progression in previous MS technology appraisals.[32-35] The European Medicines Agency also favours the use of 6-month CDP to define disability progression in their guideline on clinical investigation of medicinal products for the treatment of MS.[36] In addition, in clinical practice, determining disability progression independent of relapses in unlikely to be confirmed within three months and a longer confirmation time is required.[37] • As noted by the clinical expert in Section 3.3 of the ACD response, "*healthcare professionals are uncertain about the efficacy of interferon beta-1b, so very few people with secondary progressive multiple sclerosis take it*." The EU study, in contrast to the North American study, shows that interferon β-1b is effective at reducing the time to CDP in patients with SPMS. However, given the low uptake of Extavia® in UK clinical practice, potentially reflecting clinician's uncertainty of its effectiveness, the EU study could be considered as unreflective of the true effectiveness of interferon β-1b in the active SPMS population as seen in UK clinical practice. Overall, using the EU study, 3-month CDP MAIC for comparing siponimod with interferon β-1b results in a less reliable and more uncertain comparison, with less applicability to UK clinical practice. As such, the EU study MAIC should not be considered an appropriate source of comparative efficacy for reimbursement decisions.	section 3.7 of the FAD.
6	Consultee (company)	Novartis	**Treatment discontinuation rates should be utilised rather than study discontinuation rates** Section 3.11 of the ACD states that "*the committee considered that treatment discontinuation rather than study discontinuation would provide a better estimate of the numbers stopping siponimod in clinical practice*" The original model applied rates of study discontinuation to model stopping treatment with siponimod for any reason. Novartis agrees with this suggested change of approach and the revised model provided in support of this response has been updated to include treatment discontinuation rates instead.	Comment noted.
7	Consultee (company)	Novartis	**Utility values in the economic model should be based on Active SPMS utility values from EXPAND** Section 3.12 of the ACD states that "*the committee was concerned that the company had derived utility values from the full EXPAND population, rather than the subgroup of people with active disease. The committee concluded that utility values from the subgroup of people with active disease from*	Comment 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
			EXPAND supplemented by Orme et al. (2007) should be used in the model." Novartis agrees with this change of approach and the revised model provided in support of this response has been updated to include Active SPMS utility values from EXPAND instead of those from the ITT population. These utility values are presented alongside one another in the supporting Appendix.	
8	Consultee (company)	Novartis	**Efficacy in subgroups for people with Active SPMS with and without imaging features of inflammatory activity** Section 3.6 of the ACD states that "*it is possible to have active disease without any changes in imaging features, and that it is possible to progress in terms of changes on MRI without evidence of clinical progression. The committee was interested in whether siponimod is of more benefit in disease with imaging features of inflammatory activity than without, but the company did not explore this. The committee concluded that it is uncertain whether siponimod has the same effect in disease with and without imaging features of inflammatory activity*." In response to this uncertainty raised by the committee, three subgroups of the Active SPMS subgroup from the EXPAND trial are presented in the supporting Appendix, alongside the data for the Active SPMS subgroup: • **Relapsing SPMS with MRI activity** defined as patients with relapses in the two years prior to the study and with Gd-enhanced T1 lesions at baseline. • **Relapsing SPMS without MRI activity** defined as patients with relapses in the two years prior to the study but without Gd-enhanced T1 lesions at baseline. • **Non-relapsing SPMS with MRI activity** defined as patients with Gd-enhanced T1 lesions at baseline but without relapses in the two years prior to the study. As can be seen from the data shown in the Appendix, there are [redacted] between the subgroups in terms of effectiveness results (3- or 6-month CDP or ARR), nor in comparison to the overall Active SPMS population. By cutting the Active SPMS subgroup data into smaller subgroups, analyses are increasingly underpowered and unsuitable to determine differences between subgroups. Overall, siponimod is an effective treatment for all patients with active SPMS, regardless of their relapse or MRI status.	Thank you for your comment. The committee considered the evidence on siponimod's effects in different subgroups according to imaging features of inflammatory activity (see

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
				section 3.6 of the FAD).
9	Consultee (Professional organisation)	UK Multiple Sclerosis Specialist Nurse Association	We are concerned that most HCPs are reluctant to diagnosis SPMS due to the withdrawal of treatment or staying on sub optimal treatment	Thank you for your comment. The committee discussed the diagnosis of SPMS (see section 3.2 of the FAD).
10	Consultee (Professional organisation)	UK Multiple Sclerosis Specialist Nurse Association	We are concerned comparing Siponimod to beta interferon is counter-productive – they not comparable	Thank you for your comment. The choice of comparators was considered by the committ

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
				ee (see section 3.3 of the FAD).
11	Consultee (Professional organisation)	UK Multiple Sclerosis Specialist Nurse Association	We are concerned that the guidance contradicts the Brain Health initiative (protecting the brain and slowing progression and brain atrophy	Thank you for your comment. The committee considered the evidence on siponimod's effects on cognition (see section 3.14 of the FAD).
12	Consultee (Professional organisation)	UK Multiple Sclerosis Specialist Nurse Associatio	We are concerned that the report fails to recognise the impact and evidence of siponimod preventing the worsening of cognition which ensures people remain independent and in employment longer	Thank you for your comment. The committee considered the evidence on

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
		n		siponimod's effects on cognition (see section 3.14 of the FAD).
13	Consultee (Professional organisation)	Association of British Neurologists	We are grateful for the opportunity to comments on the appraisal consultation document. Siponimod for treating secondary progressive multiple sclerosis. Our response is as follows:- Has all of the relevant evidence been taken into account? Yes Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? No Whilst we agree that not many patients with active SPMS will be on a beta-interferon, there will be some. Most will still be on a higher potency treatment which will carry a greater total cost (to include infusions and monitoring). There will be the additional journeys to the hospital for both patients and their cares which, at this moment in time, we should be making great efforts to limit. It is appreciated that the use of these higher potency therapies may not strictly be within the guidance, however it reflects real world practice and therefore cost calculations should accommodate it. All of these patients will already be under the care of a specialist and be undergoing regular MRI surveillance. Are the recommendations sound and a suitable basis for guidance to the NHS? No For reasons above. 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	Thank you for your comment. The committee considered the choice of comaparators and the healthcare resource use of siponimod and comparators (see sections 3.3 and

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
				3.12 of the FAD).
14	Consultee (Patient organisation)	MS Society	**Lack of treatment options is a huge problem for people with SPMS** Karen told us "I was diagnosed with Relapsing Remitting MS in September 2008, and my condition has deteriorated since then, eventually leading to me needing to use a wheelchair since 2013. I was eventually diagnosed with SPMS in 2014. As there were no available treatments I opted to take part in the Siponimod clinical trial. Progression seemed to immediately slow until the trial had to be put on hold for 8 months while the required approvals were provided to the study. In this time my condition deteriorated further until the trial was approved and I was allowed to get back on the drug! This drug has been essential to slow progression of my condition. I dread to think what my condition would be like if Siponimod was not available!" Fiona told us "I was diagnosed with MS nearly 5 years ago. I only had 6 months before being told my MS was secondary progressive and there was no treatment. I have always been a very independent person, caring for my mother for twenty years until her death about a year and a half before my diagnosis. My husband has suffered from a neurological condition for almost 30 years and depends on me to do the domestic tasks around the house. Any drug that could halt the progression of the debilitating disease that MS is would be a major improvement for me and many others whose mobility and ability to function is greatly impaired." Catherine told us "I have some I have active lesions but no treatment. I use a wheelchair outdoors and a stick and furniture support indoors. I do not want to reach the point of using a wheelchair indoors my house is old and not good for a wheelchair. My future is a dark place I try not to think about because I have no treatment." Margaret told us "I have been using Rebif (interferon beta 1-a) for MS since 2008. I inject three times per week and, as I have been injecting for twelve years, I have developed lesions in some injection site areas. I am concerned that I will no longer have sites in which to inject. Rebif helped me to work as a teacher for 18 years since diagnosis (until I took early retirement last year in 2019) and it has helped me to continue driving. An oral medication would make a HUGE difference to my life. I urge NICE to promote the use of Siponimod. Jacqueline, patient expert for the NICE siponimod committee told us: "I have lived with SPMS since a diagnosis four and a half years ago following years of RRMS. An occasional wobble, wonky eye sight and the odd UTI has turned into a body limp with immobility, repeated UTIs, a mind so fretful and confused that I flare up even at the smallest of blips, and bouts of trigeminal neuralgia - a pain so shocking it ravages my very being. If that isn't a sign of active disease, I don't know what is! I can no longer walk beyond 100 metres, albeit with my walking stick as my constant companion, I fear to be replaced by the wheelchair if nothing is done. My family and friends feel so helpless as they see my once active, sociable and positive minded human being turn into a shrunken shadow of its former self. They find my situation even more frightful given that there is a well-tested and tried drug out there, already licensed across Europe, USA, Asia and Australia that could transform lives of people with active SPMS like myself."	Thank you for your comment and for sharing the stories of people with SPMS. The committee was aware of the lack of treatment options available for people with SPMS (see section 3.1 of the

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
				FAD). The views of clinical experts and patient/ carer representatives were considered by the Appraisal Committee when formulating its recommendations.
15	Consultee (Patient organisation)	MS Society	**The tablet form is far preferable to injectable alternatives** Pamela told us “I was giving myself injections of interferon for around 5 years. I would certainly have preferred a daily tablet to finding a new site to stab yourself! I have had secondary progressive MS for the past 10 years and am now having to use a wheelchair”. Rhona told us “I'm losing control of my left hand and my fingers are getting crooked. I have severe and painful spasms and cramps. I can't contemplate injections so this is my only chance of medication.” Margaret told us “I have been using Rebif (interferon beta 1-a) for MS since 2008. I inject three times per week and, as I have been injecting for twelve years, I have developed lesions in some injection site areas. I am concerned that I will no longer have sites in which to inject. Rebif helped me to work as a teacher for 18 years since diagnosis (until I took early retirement last year in 2019) and it has helped me to continue driving. An oral medication would	Thank you for your comment. The committee discussed the potenti

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
			make a HUGE difference to my life." Gillian told us "I have secondary progressive MS and have been on DMTs for 12 years, all by injection. I find the injections still painful at times and they have left my skin lumpy and unsightly. I find it difficult to find injectable sights after all these years. A tablet form would be so much easier and less stressful, hopefully my skin would recover too. Even if a tablet is too late for me it would really help those starting on therapy." Julie has been told by her consultant that siponimod would be an option for her and is devastated it may not be available. Julie told us "I suffer from secondary progressive MS and this is devastating news as Siponimod was my only hope of slowing the rate of disability which continues to deteriorate. My MS is active, I had a big relapse last November and spent a month in hospital with my MRI scans showing a lot of information. My consultant said Siponimod would be an ideal option for me. I have issues using my right hand so would find injections really difficult, I have no strength in that hand. Siponimod 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. It would also allow me to continue with part-time working to support myself for longer rather than needing to look for state help. It is very disheartening to think that finally there is a drug that will have involved much hard work and money to develop in order to help those with active progressive secondary ms which it has now been decided we are not going to be given the chance to benefit from."	al benefits of siponimod being an oral treatment (see section 3.14 of the FAD). The views of clinical experts and patient/carer representatives were considered by the Appraisal Committee when formulating its recommendat

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
				ions.
16	Consultee (Patient organisation)	MS Society	**Siponimod was effective for people who were on the trial** Sally told us “I was given the chance to take part in the siponimod trial because I met the criteria and took part for over 5 years. It certainly slowed down the progression of my SPMS. I had to come off it because I was diagnosed with early stage breast cancer and I noticed a marked acceleration in my MS once I had not been taking the drug for about a year.” Kay-Anne told us “I was on the clinical research trial for siponimod. I felt stronger and more able to push the limits of my ability without feeling utterly exhausted afterwards, although I wasn't sure if that was the placebo effect. When the trial stopped, my abilities, especially walking (I use two crutches) became harder, slower and more sluggish. They required more energy leaving me less to manage on, which lowered my mood. This was when I suspected I had been on the drug which was later confirmed by the research team. Being on siponimod had helped almost stabilise my symptoms and slowed their worsening. It had given me the ability to manage and gave me hope that my difficulties would not deteriorate too quickly. For someone with MS that hope is essential.”	Thank you for your comment. The committee discussed results from the EXPAND trial and considered siponimod to be an effective treatment compared with placebo for active SPMS (see section 3.5 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
				The views of clinical experts and patient/ carer representatives were considered by the Appraisal Committee when formulating its recommendations.
17	Consultee (Patient organisation)	MS Society	**The MS Society has heard sustained anecdotal evidence that neurologists are reluctant to diagnose SPMS because of the lack of effective treatments** While the prevalence of this practice is very difficult to measure accurately, we have heard consistently form both neurologists and people with MS that diagnoses are delayed because neurologists believe, based on evidence from their own clinical practice that patients continue to derive great benefit from these DMTs. The situation is further complicated because diagnosis of SPMS is not straightforward, as the clinical expert describes in paragraph 3.2 of the ACD. However, overall our experience would support the view that having an effective treatment for active SPMS could lead to earlier diagnosis of SPMS in many cases (as noted in paragraph 3.2 of the ACD).	Thank you for your comment. Comment noted.
18	Cons	MS	**MS Society data demonstrates that some people with SPMS are taking DMTs for relapsing remitting MS**	Thank

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
	ultee (Patient organisation)	Society	In our My MS My Needs 3 survey in 2019, only one person with active secondary progressive MS reported using Extavia, the only DMT licensed explicitly for active SPMS, out of 936 respondents with active secondary progressive MS in the UK. The survey found that it was more common for people with SPMS to be on DMTs that are not licensed explicitly for active secondary progressive MS. For example, 33 people told us they were taking other interferons (aside from Extavia), 28 people said they were taking Tecfidera, and 23 people Tysabiri. This corroborates the assertion from the clinical expert quoted at paragraph 3.3. of the ACD that “disease-modifying therapies are sometimes used outside of their licensed indications in people with secondary progressive multiple sclerosis during the transition period from relapsing–remitting disease.” This point was further corroborated by some of the people with SPMS who told us their stories as part of this consultation. Yvonne told us “I was diagnosed with relapse-remitting MS in 1998 at the age of 22. Unfortunately my condition has deteriorated over the past few years whilst still having occasional relapses, and it was confirmed in September 2019 that I have secondary progressive MS. I am concerned that no easy to-make medication is available to treat this as I have very little use of my hand. I am still taking Tecfidera for my RRMS, but live with such uncertainty of what the future holds for me and my SPMS” Overall, we feel it would be appropriate to consider the effectiveness of Siponimod against other DMTs rather than best standard of care alone.	you for your comment. The committee was aware of the lack of treatment options available for people with SPMS (see section 3.1 of the FAD). The choice of comparators was considered by the committee (see section 3.3 of the

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
				FAD). The views of clinical experts and patient/ carer representatives were considered by the Appraisal Committee when formulating its recommendations.
19	Consultee (Patient organisation)	MS Trust	The MS Trust is extremely disappointed that NICE is unable to recommend siponimod as an NHS treatment for active secondary progressive MS. We note that the committee recognises that siponimod is a clinically effective treatment for active secondary progressive MS but 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.	Thank you for your comment. Following the revised analyses

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
				submitted by the company in response to consultation, the committee considered siponimod to be cost-effective (see section 3.16 of the FAD), so the treatment has been recommended. The views of clinical experts

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
				and patient/ carer representatives were considered by the Appraisal Committee when formulating its recommendations.
20	Consultee (Patient organisation)	MS Trust	**Huge unmet need** We wish to emphasise the huge unmet need for a treatment which will slow down progression in active secondary progressive MS (SPMS). Our announcement of NICE's initial decision to reject siponimod for SPMS was greeted by bitter disappointment from our supporters. In the absence of a cure, the biggest unmet need for people with SPMS is a treatment which can slow down or stop progression of disability. As a progressive condition, SPMS has an impact on all aspects of life – physical, emotional, social and economic. These profoundly affect not only the person diagnosed with SPMS, but their families as well. Transitioning to SPMS is a frightening and unwelcome milestone in the course of MS. The reality for people living with this condition is that this represents the point at which current treatment with disease modifying drugs is withdrawn, contact with MS specialist health professionals is significantly reduced while increasing disability and loss of independence become major concerns. Before preparing our appraisal submission to the committee, we conducted a survey to gather the views of those affected by SPMS. We received 383 responses (29 August – 17 September 2019) from people with SPMS, their families and specialist MS health professionals. Our submission to the appraisal included statistics and direct quotes from the survey, providing a powerful testimony. Their experiences provide a valuable personal perspective on living with SPMS, the impact it has on quality of life, and their perception of siponimod. Time and again respondents to our survey commented that there is currently no treatment to delay the progression of SPMS, nothing that can change the	Thank you for your comment. Following the revised analyses submitted by the company in response to consult

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
			prognosis of their condition. Many people are doing all that they can to minimise the impact of SPMS, but they are all too aware that there is nothing that will slow down the progression of their disease. The benefits of slowing down progression are seen as maintaining mobility and independence for longer, allowing people to continue to work for longer, and saving costs for the NHS in the long term by preventing progression and the need for MS services and social care. These two quotes, taken from the MS Trust appraisal submission illustrate the impact on peoples' lives. • *I've had to give up my career of 10 years as a Paramedic, which I adored. I am fighting to stay at work, in an alternative role, but without treatment my working life will, undoubtedly, soon be coming to an end, which will completely crush me.* • *I am a single, widowed mother with SPMS - just 5 years ago I didn't know I had MS and now I am reliant on a wheelchair. My son is 12. The progression of my MS has not only resulted in my care needs increasing but also meant my son has required additional intervention and support.*	ation, the committee considered siponimod to be cost-effective (see section 3.16 of the FAD), so the treatment has been recommended. The committee was aware of the lack of treatment options available for people with

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
				SPMS (see section 3.1 of the FAD). The views of clinical experts and patient/ carer representatives were considered by the Appraisal Committee when formulating its recommendations.
21	Consultee (Patient organisati	MS Trust	**Secondary progressive MS and MRI scans** The committee recognises that secondary progressive MS is a continuum of relapsing remitting MS and notes that diagnosis is based on signs and symptoms rather than biochemical or radiological testing. The marketing authorisation for siponimod limits its use to active disease which requires evidence of <u>either</u> relapses <u>or</u> MRI inflammatory activity; neither of these is mandatory or considered to be a more reliable indicator of active SPMS.	Thank you for your comment. The committ

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
	on)		However, the ACD then goes on to discuss the need for an MRI to confirm diagnosis of active SPMS. In practise, over a period of many months, a neurologist (and the person with MS) will notice increasing disability and interpret this as an indicator that relapsing remitting MS is transitioning to SPMS. Diagnosis of SPMS is retrospective and there are no definitive biomarkers or imaging tests that can be used to aid diagnosis; an MRI would not be use routinely to diagnose SPMS. In fact, it is quite likely that someone who is transitioning from relapsing to SPMS will not have had an MRI for some years. A relapse on top of increasing disability is sufficient to diagnose active SPMS; an MRI should not be necessary in this situation. While an MRI scan may be necessary to identify active disease in the absence of a relapse, it should not be mandatory in the presence of a relapse. Concerns about resource impact of additional MRI scans should be reviewed in the context of the introduction of ocrelizumab for primary progressive MS. Eligibility for ocrelizumab requires evidence of MS activity on an MRI scan; in practice, NHS teams have been able to exclude those who are not eligible based on other criteria, with the result that MRI screening has been minimised and the introduction of this treatment has not had as great an impact on services as was anticipated.	ee considered the company's approach to modelling neurology appointments and MRI scans (please see section 3.12 of the FAD).
22	Consultee (Patient organisation)	MS Trust	**Comparators – interferon beta 1b** It is widely acknowledged by clinical experts and NHS commissioners that because there are no treatments for SPMS, clinicians delay diagnosis and continue to prescribe all of the disease modifying drugs beyond the transition from relapsing remitting to secondary progressive MS. A survey of UK MS neurologists and nurses revealed that the most common reason for reluctance to diagnose SPMS was withdrawal of disease modifying drugs[1]. It is also acknowledged that interferon beta-1b, the only treatment licensed for SPMS with active disease, is taken by just 75 people in England. Prescribing of interferon beta 1b (Extavia) is very low, especially in people with active secondary progressive MS; it is self-injected and is supplied as solvent and powder which must be made up each time it is taken. The Patient Information Leaflet for Extavia details the seventeen step instructions for doing this. People with manual dexterity, visual or cognitive difficulties, all of which are common problems in secondary progressive MS, will find this very difficult, if not impossible, to do. The conclusion of the committee that "some people with active secondary progressive multiple sclerosis take interferon beta-1b but most people have no disease-modifying treatment" may reflect policy but it certainly does not reflect practise. On the contrary, people with active secondary progressive would be highly likely to be taking one of the disease modifying drugs.	Thank you for your comment. Following the revised analyses submitted by the company in

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
			For an accurate picture of the current cost to the NHS of treating active secondary progressive MS, this appraisal must recognise that established clinical management includes all of the disease modifying drugs at least up until an established EDSS 7, even though this is outside of marketing authorisation. As a minimum, a blended comparator of disease modifying drugs based on UK market share should be used to properly reflect the true cost to the NHS of current treatments used for active SPMS. Failure to approve siponimod for NHS treatment of active SPMS will result in continued use of disease modifying drugs which have not been demonstrated to be effective against progression in SPMS and represent a significant cost to the NHS.	response to consultation, the committee considered siponimod to be cost-effective (see section 3.16 of the FAD), so the treatment has been recommended. The choice of comparators was considered by the committ

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
				ee (see section 3.3 of the FAD). Considerations about cost effectiveness are explained in the Guide to the methods of technology appraisal section 6.2.13–6.2.19.
23	Consultee (Patient organisation)	MS Trust	**Comparators - best supportive care** The committee concludes that best supportive care is a relevant comparator. We do not believe this is correct, in reality the population most likely to be eligible for siponimod will be taking one of the disease modifying drugs. Best supportive care was initially included in the draft scope but subsequently removed from the final scope in response to stakeholder comments. The final scope included established clinical management, including disease modifying therapies used outside their marketing authorisation. As noted in comment 4 above, a blended comparator of disease modifying drugs based on UK market share should be used to properly reflect the true cost to the NHS of current treatments used for active SPMS.	Thank you for your comment. The choice of comparators

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
			Best supportive care is not defined in the ACD, nor are costs provided, so it is impossible for us to comment on the composition and level of NHS services that is assumed to be available across England and Wales. There is currently no research or professional consensus on what best supportive care for SPMS might be or how much it might cost. The concept of best supportive care is idealistic. It is unrealistic to assume that all people with MS have access to high quality care that fully meets their needs. The reality is that people with MS often have very limited access to services. It is clear from the data collected in our survey that people with SPMS have a high level of need for NHS care. Given the wide range of symptoms that people with SPMS may experience, it is important that there is access to a range of therapies delivered by skilled health professionals, competent in MS care. In reality, access to NHS and social care interventions such as physiotherapy or neurorehabilitation are limited, sporadic or even non-existent. Calculation of the cost of providing best supportive care cannot assume an ideal situation where these services are readily available. We are aware that people with SPMS are often 'discharged' from MS services, either due to a perception that there is no treatment available for SPMS or due to limitation in service capacity. Overwhelmingly, the message that people receive from MS health professionals is that there is no treatment available for SPMS. The quality of and access to care is highly dependent on where an individual lives. An MS Society report found that 40 per cent of MS specialist centres failed to offer people with MS a truly multi-disciplinary clinic[1]. This was also reflected in the Royal College of Physicians national audit of services for people with MS which found only 43% of people said they knew they had access to specialist neuro rehabilitation and 57% said that they had access to specialist MS physiotherapists[2]. In 2011 the National Audit Office report for services for people with neurological conditions found that the case loads of MS nurses varied extensively in each Strategic Health Authority[3]. A survey[4] conducted by the MS Trust in 2016 found that on average, people with progressive MS are seeing MS specialists much less often than people with relapsing MS. People with SPMS and their families go to great lengths to remain active and independent and do whatever they can to stay in work. This often involves paying privately for treatments with limited availability through the NHS, such as Sativex, physiotherapy or chiropody, or treatments which are not available at all, such as Fampyra. This further demonstrates that, on the ground, "best supportive care" does not meet the needs of people with SPMS. We do not believe that modelling accurately reflects the true experience of NHS treatment for many people with SPMS and that, for some people, progression is more rapid due to limited availability of care.	was considered by the committee (see section 3.3 of the FAD). The committee was aware of the lack of treatment options available for people with SPMS (see section 3.1 of the FAD). The views of clinical experts and

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
				patient/ carer representatives were considered by the Appraisal Committee when formulating its recommendations.
24	Consultee (Patient organisation)	MS Trust	**Innovation** The committee questions the innovative nature of siponimod. There are a number of aspects of siponimod treatment which have not been captured within the cost effectiveness calculations. Siponimod is the first oral drug to show a reduction in disability progression in active secondary progressive MS. An effective treatment for people with secondary progressive MS would be truly life changing. The availability of a treatment for secondary progressive MS will provide hope for people diagnosed with this type of MS and will lead to a more optimistic and constructive interaction with neurologists and improved quality of life not captured by clinical trial EQ5D measures. Siponimod is taken orally once daily at home, a route of administration which is generally preferred by patients, leads to good adherence and has low impact on NHS services. It is also anticipated that monitoring requirements (for example blood and urine tests) for siponimod will be moderate with low impact on NHS services. In addition to its effect on disability progression, siponimod has been shown to improve cognitive performance as measured by the Symbol Digit Modalities Test. Slower performances on SDMT correlate well with activities of daily living and employment status; impaired performance on SDMT in people with MS has also been linked to decline in financial income, independently of physical disability. Our survey asked people with SPMS how the condition affected	Thank you for your comment. The committee discussed the potential benefits of siponimod being an oral

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
			them physically; out of 235 responses to this question, 56% reported cognitive problems. An improvement in cognitive function would offer a significant benefit to people with active secondary progressive MS, allowing them to remain in work for longer and maintain family and social relationships for longer.	treatment (see section 3.14 of the FAD). The committee considered the evidence on siponimod's effects on cognition (see section 3.14 of the FAD).
25	Consultee (Patient organisation)	MS Trust	**Conclusion** The MS Trust wishes to state in the strongest possible terms the potential benefits of siponimod for active SPMS in terms of meeting the huge unmet need, delaying disease progression, and the impact on the daily lives of this group of people. Although people do all that they can to minimise the impact SPMS has on their lives, they are all too aware that there is nothing that will slow down the progression of their disease. As well as the long-term impact on mobility, work and independence, the psychological impact of a future with SPMS should not be underestimated. Our research has highlighted that the message people received from MS health professionals is that there is no treatment available for SPMS, which adds to that burden. The introduction of disease modifying drugs for relapsing remitting MS has been the catalyst for significant improvements in MS services for people with	Thank you for your comment. Following the revised analyses submitt

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
			relapsing MS. The introduction of a treatment for active SPMS would similarly result in a greater focus on services for progressive MS and a more pro-active approach to managing SPMS which would ultimately benefit a much wider group of people than just those who might be eligible for siponimod.	ed by the company in response to consultation, the committee considered siponimod to be cost-effective (see section 3.16 of the FAD), so the treatment has been recommended. The views of clinical experts and

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
				patient/ carer representatives were considered by the Appraisal Committee when formulating its recommendations.
26	Web comment (public)	(Web commenter 1)	I am at a worse loss now if that could ever be thought possible in my SPMS daily nightmare. Since progressing from RR I have been offered and so not received any treatment, care or consideration, I feel completely ignored and useless with little impetus to continue with this existence, it's no longer a life, all I achieved has been rendered useless. Thanks for evermore nothingness	Thank you for your comment. The views of clinical experts and patient/ carer representatives were considered by the Apprais

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
				al Committee when formulating its recommendations.
27	Web comment (public)	(Web commenter 2)	**Has all of the relevant evidence been taken into account?** One of the points about Siponimod was that it would have an impact on the NHS workforce mainly in relation to MRI increase scanning that would be required for seeking eligibility for this medication, however this should not be a prerequisite for this drug as you rightly point out that it would lead to increased scanning but this scanning would be potentially unnecessary. Many people have clear clinical relapses that do not need a scan but due to rigors of having to prove that a medication should be given Neurologists are scanning far more than is strictly necessary. MRI's don always pick up relapses and do not always show cognitive relapses. A way that the NHS would be impacted by Siponimod would be to allow people with SPMS a medication for their condition that they have not truly had before, interferon beta in the form of Extavia is a very poor medication for them as it is given on alternate days and causes fatigue and flu like symptoms and is a poor devise for administration. Why would people who have high levels of fatigue and potentially struggling to hold onto their careers want to administer a medication with these side effects. We have no one on this medication in my clinic as it is so poorly tolerated. However the people on the clinical trial we have on Siponimod have a few side effects at the start of the medication and are happy to continue on it as it has no continuing side effects.	Thank you for your comment. The committee considered the company's approach to modelling neurology appointments and MRI scans (please see section 3.12 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
				The committee discussed results from the EXPAND trial and considered siponimod to be an effective treatment compared with placebo for active SPMS (see section 3.5 of the FAD). The committee discuss

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
				ed the potential benefits of siponimod being an oral treatment (see section 3.14 of the FAD).
28	Web comment (public)	(Web commenter 2)	**Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?** Probably but I do think comparing siponimod with Extavia is a poor comparison as the side effects on people with MS do not allow it to be used frequently. Comparing any drug with no available medication is bound to be expensive. My understanind is that siponimod has a good effect on cognitionbut this is not mentioned.	Thank you for your comment. The choice of comparators was considered by the committee (see section 3.3 of the FAD). The committ

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
				ee considered the evidence on siponimod's effects on cognition (see section 3.14 of the FAD).
29	Web comment (public)	(Web comment er 2)	**Are the recommendations sound and a suitable basis for guidance to the NHS?** I do understand that cost has to be considered in the NHS it is essential, but 2 of the people on Siponimod on our clinical trials have been able to increase their hours of work and are therefore contributing to society which I cannot see that has been included in the recommendations. The guidance is not suitable for the NHS as when people with MS realize that this medication has been turned down for use we will be inundated by calls asking us why they cannot have this medication. This is a hidden impact of the decision to reject this drug but has a huge impact on my workload. Obviously if it is recommended tis would require extra clinic time which in turn would have a big impact on my service but that would be accommodated as fingolimod was. That medication is one that is well tolerated and can be supported within the NHS well.	Thank you for your comment. Following the revised analyses submitted by the company in response to consultation, the committ

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
				ee considered siponimod to be cost-effective (see section 3.16 of the FAD), so the treatment has been recommended. Considerations about cost effectiveness are explained in the Guide to the methods of technology

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
				appraisal section 6.2.13–6.2.19. The views of clinical experts and patient/carer representatives were considered by the Appraisal Committee when formulating its recommendations.
30	Web comment (public)	(Web commenter 2)	**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?** More women are affected with SPMS than men and more will have hidden disabilities which may be seen as not being so important and therefore not worth doing anything about, but siponimod can and I have seen it slow down the progression of MS in my small number of people I have on this medication and I would recommend people with active SPMS and who are still able to walk with bilateral support to put themselves forward for testing. If it is turned down it	Thank you for your comment.

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
			could be seen as being sexist and discriminatory to people with disabilities.	Please see the Equalities Impact Assessment for discussions about discrimination.
31	Web comment (public)	(Web commenter 3)	**Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?** No.	Thank you for your comment. Comment noted.
32	Web comment (public)	(Web commenter 3)	**Are the recommendations sound and a suitable basis for guidance to the NHS?** No.	Thank you for your comment. Comment noted.
33	Web comment (public)	(Web commenter 3)	As you have recognised, take up of Interferon beta-1b (IB1b) is low. I think it is important to note that IB1b is not suitable for many patients with secondary progressive MS where cognitive function is affected, and it is in turn not offered. Making a recommendation on the lack of comparative study with existing treatment options ignores the needs of many. Furthermore, were a comparative study carried out, it is likely it would not reflect the wide spectrum of MS patients due to the limited take up.	Thank you for your comment.

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 noted.
34	Web comment (public)	(Web commenter 3)	This is not always offered, I know of a patient that after returning from living abroad as a diplomatic spouse, was not seen by a consultant for 12 years. This was only organised when symptoms were noticeably declining through GP referral (which took a further 2 years). They have now been diagnosed with SPMS and never had the opportunity to try other therapies before this stage.	Thank you for your comment. Comment noted.
35	Web comment (public)	(Web commenter 3)	It is heartbreaking that this is a decision based on economic cost-effectiveness rather than quality of life of patients. Committee papers themselves state "Siponimod offers patients with SPMS, clinicians, and the NHS a step-change in therapy, addressing for the first time their need for a DMT by offering them a treatment with proven efficacy on disability progression in SPMS." (B. 2. 13. 3)	Thank you for your comment. Following the revised analyses submitted by the company in response to consultation, the committee considered

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
				siponimod to be cost-effective (see section 3.16 of the FAD), so the treatment has been recommended.
36	Web comment (public)	(Web commenter 3)	I have considered the evidence submitted, and one detail from the MS Society that I wanted to raise. The answer to Q10 (disadvantages of the technology) tells of a patient that struggles with blister packaging and it is noted that patients with cognitive problems, such as executive dysfunction, may struggle to administer a daily medication. One successful mitigation to both of these arguments is the availability of 'Medi-packs'. Their answer to Q15 (bullet 3) also adds weight that the recommendation on cost-effectiveness may not be robust.	Thank you for your comment. Comment noted.
37	Web comment (public)	(Web commenter 3)	Surely the expert research outcomes should be given more weight than the committee's preferences. When it comes to denying treatment for many who would otherwise have an improved quality of life.	Thank you for your comment. Comment noted.
38	Web com	(Web com	**Has all of the relevant evidence been taken into account?** No ... the number of people affected with SPMS is incorrectly stated.	Thank you for

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
	ment (public)	ment er 4)		your comment. We have updated the FAD accordingly (see section 3.3).
39	Web comment (public)	(Web comment er 4)	**Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?** No, the benefits of delaying disease progression are not considered in this report.	Thank you for your comment. The views of clinical experts and patient/ carer representatives were considered by the Appraisal Committee when formulating its

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
				recommendations.
40	Web comment (public)	(Web commenter 4)	**Are the recommendations sound and a suitable basis for guidance to the NHS?** No. The recommendations are requesting further trials when there is sufficient evidence to approve this drug as there is evidence of a delay in disease progression being achieved.	Thank you for your comment. Comment noted.
41	Web comment (public)	(Web commenter 4)	**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	Thank you for your comment. Comment noted.
42	Web comment (public)	(Web commenter 4)	This recommendation should be urgently amended. siponimod had a (?) probability of being the most cost-effective option at a willingness-to-pay threshold of £30,000/QALY. 75,000 people are (or will be) affected by SPMS. This population need hope at a time when their future hopes are being ripped away as they progress in their disease. Delaying disease progression is of the utmost importance and Siponimod offers this potential. Here are comments on the Committee discussion: Subsection 3.3 Where has the estimate of 9000 people with SPMS come from? There is no accurate data but if I am surmising from the 'forgotten many' report, the true numbers could be: 130k people diagnosed with MS in UK. Of these 85% are RRMS from which 2/3 are estimated to develop SPMS. My maths indicate 73k people might transition to SPMS in the UK.	Thank you for your comment. Following the revised analyses submitted by the company in respon

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
			Subsection 3.5 Confirms that Siponimod is beneficial Compared to placebo in active secondary progressive population … So it is of benefit in cases of active disease. Subsection 3.6 The interest in imaging features is irrelevant to the life of a person with MS. The EDSS is the only way to assess the impacts. Therefore this consideration might be interesting to a clinician, but surely that is not the purpose of a disease modifying therapy? The individual writing this comment has a profuse spread of old disease activity on her MRI, but doesn't show a EDSS progression. Please do not insist on seeing imaging activity when making a decision on drug efficacy. Subsection 3.7 "The committee concluded that there were substantial uncertainties associated with all of the indirect comparisons." Is irrelevant when all data sets favour Siponomid over Betaferon. Subsection 3.8 However in the absence of like for like comparison, the beneficial results in Europe prove a case to make Siponimod available in the UK. The fact that EMA and FDA have approved indicate there is enough data to decide now. You do realise that every day counts for a person with MS? Subsection 3.11 This is more useful for the future once people with MS are using Siponimod. It does not affect a decision on whether the drug has benefits sufficient to justify approval. Subsection 3.13 In the recently published "The Forgotten Many" (June 2020) the paper refers to the costs associated with MS correlating with disease severity. Therefore, approval of a drug that delays the progression of disease severity (such as Siponimod) would reduce the costs per patient. This would more than offset the additional neurology visits and a once per year MRI scan. Subsection 3.14 The waning effect for a different drug which is used in the relapsing phase of disease is not comparable to the waning in a drug which is used for people with SPMS. The disease course is on a different trajectory at this point. Therefore it might be useful to model the incomparable data, but it is not necessary within the scope of approval for this drug which is to be marketed to a different population. Subsection 3.15 Most of the preferences in this section are not relevant to making a decision because, as pointed out in comments on the previously subsections, these factors are not necessary to reach an informed decision. The decision paper states "include the costs of neurology appointments and MRI scans for people starting siponimod" but this needs to also include the benefits of slower disease progression and the resultant impact on lower impact on GPs, hospital admissions, care facilities, DSS benefits. (Or maybe delete this preference from the document?).	se to consultation, the committee considered siponimod to be cost-effective (see section 3.16 of the FAD), so the treatment has been recommended.

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
43	Web comment (public)	(Web commenter 4)	Where has the estimate of 9000 people with SPMS come from? There is no accurate data but if I am surmising from the 'forgotten many' report, the true numbers could be: 130k people diagnosed with MS in UK. Of these 85% are RRMS from which 2/3 are estimated to develop SPMS. My maths indicate 73k people might transition to SPMS in the UK.	Thank you for your comment. We have updated the FAD accordingly (see section 3.3).
44	Web comment (public)	(Web commenter 4)	However in the absence of like for like comparison, the beneficial results in Europe prove a case to make Siponimod available in the UK.	Thank you for your comment. Comment noted.
45	Web comment (public)	(Web commenter 5)	**Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?** Summary of cost effectiveness is not reasonable as it compares siponimod to a treatment that is not widely used and does not consider the wider economic case of treatment	Thank you for your comment. The choice of comparators was considered by the committ

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
				ee (see section 3.3 of the FAD).
46	Web comment (public)	(Web commenter 5)	The committee are comparing siponimod to beta interferon despite noting that beta interferon is rarely prescribed for secondary progressive MS. Instead the committee should compare siponimod to no treatment taking into account the economic cost of increased disability to society	Thank you for your comment. The choice of comparators was considered by the committee (see section 3.3 of the FAD).
47	Web comment (public)	(Web commenter 5)	Siponimod is currently subject to an ongoing open label extension. This trial is likely to gather evidence that may address the gaps identified by the committee. The review date should be bought forward to the anticipated date when further information will be available	Thank you for your comment. Following the revised analyses submitted by

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 company in response to consultation, the committee considered siponimod to be cost-effective (see section 3.16 of the FAD), so the treatment has been recommended.
48	Web comment (public)	(Web commenter 6)	**Has all of the relevant evidence been taken into account?** Impact in cognitive function not considered enough	Thank you for your comment. The committee conside

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
				red the evidence on siponimod's effects on cognition (see section 3.14 of the FAD).
49	Web comment (public)	(Web commenter 6)	**Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?** Unrealistic to think that active comparator is no DMT or Beta 1b	Thank you for your comment. The choice of comparators was considered by the committee (see section 3.3 of the FAD).
50	Web comment (public)	(Web commenter 6)	**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	Thank you for your comment.

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 noted.
51	Web comment (public)	(Web commenter 6)	the majority of people being considered for siponimoid would be having regular MRI's due to the requirements of other DMT's.	Thank you for your comment. Comment noted.
52	Web comment (public)	(Web commenter 6)	It is my opinion that in the real world many SPMS patient with EDSS less than 6.5 will be continuing on a DMT and therefore the active comparator to siponimoid in terms of cost is not 'no treatment'. Diagnosing someone with SPMS is not clear cut and often requires observation over many months or even years. Due to this difficulty in diagnosis and the possibility of a transition period where relapses are still possible, patients and health care professionals often choose to be caution in stopping DMT and the patient remains on when it is likely they are no longer RRMS. Another current factor is a patients reluctant to stop a DMT when their are no other options for SPMS. In my experience Interferon beta-1b is not a treatment prescribed for SPMS.	Thank you for your comment. The choice of comparators was considered by the committee (see section 3.3 of the FAD).
53	Web comment (public)	(Web commenter 6)	Cognitive changes in MS are very common and often one of the symptoms that patients reports is the most difficult and frustrating to live with. It is often cognitive decline that will lead to the decision to stop working. In the appraisal there was no consideration to the impact siponimoid could have on slowing this cognitive decline. The clinical trails had a possible effect on brain volume loss and cognitive processing speed.	Thank you for your comment. The

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
				committee considered the evidence on siponimod's effects on cognition (see section 3.14 of the FAD).
54	Web comment (public)	(Web commenter 7)	I have trouble with this argument as the patients start the DMT during the relapsing phase of MS. Then it is very difficult to know whether/ when they have entered SPMS with certainty. It is therefore inevitable that some people remain on those DMTs during SPMS even though they may not be commissioned to start in people with SPMS.	Thank you for your comment. Comment noted.
55	Web comment (public)	(Web commenter 7)	I agree that this effect has been rather downplayed in the appraisal and is of high relevance to people with MS. It is a common and disabling symptom that has a considerable impact on independence. It may be worthy of greater consideration.	Thank you for your comment. Comment noted.
56	Web comment	(Web comment	**Has all of the relevant evidence been taken into account?** Mention is made of Beta-Interferon as an alternative drug but no account appears to have been taken of the significant increase in convenience of Siponimod (in tablet form) over Beta-Interferon (requiring a solution to be mixed and self-injected, both activities becoming increasingly difficult for a patient	Thank you for your

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
	(public)	er 8)	losing mobility/ feeling in hands).	comment. The committee discussed the potential benefits of siponimod being an oral treatment (see section 3.14 of the FAD).
57	Web comment (public)	(Web commenter 8)	**Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?** The consultation document is silent on the loss of tax revenue to the exchequer in the event of the carer having to give up or reduce employment hours in addition to that of the patient's. It is also silent on the likely increase in monetary state benefits payable such as Personal Independence Payments made to MS patients experiencing increasing mobility loss and daily living issues (disability). The cost of Beta-Interferon as a comparable has also not been mentioned although one may infer that it is cheaper.	Thank you for your comment. Comment noted. Considerations about cost effectiveness

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 explained in the Guide to the methods of technology appraisal section 6.2.13–6.2.19.
58	Web comment (public)	(Web commenter 8)	**Are the recommendations sound and a suitable basis for guidance to the NHS?** Don't feel qualified to answer this as a lay person - I have responded as an interested person given that I am suffering from SPMS.	Thank you for your comment. Comment noted.
59	Web comment (public)	(Web commenter 8)	**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?** On the grounds of disability it should be noted that mixing a solution and self-injecting such as is required for Beta-Interferon is much more difficult for a disabled patient than an able-bodied patient. This should be compared with Siponimod which can be taken in tablet form (I currently have no problem swallowing).	Thank you for your comment. Please see the Equalities Impact Assess

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
				ment for discussions about discrimination. The committee discussed the potential benefits of siponimod being an oral treatment (see section 3.14 of the FAD). The views of clinical experts and patient/carer represe

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
				ntatives were considered by the Appraisal Committee when formulating its recommendations.
60	Web comment (public)	(Web comment er 9)	**Has all of the relevant evidence been taken into account?** I would suggest that it is wrong to consider that most patients with secondary progressive are not on a disease modifying treatment. There has been little study on the effects of stopping disease modifying treatments in secondary progressive multiple sclerosis but most MS clinicians will have experienced deleterious outcomes in many patients who have come off disease modifying treatment and will thus be reluctant to recommend stopping treatment until patients are advanced in disability or to even classify secondary progressive disease until a much later time point in the condition. If siponimod were made available as a treatment then this may allow clinicians to treat patients with early secondary progressive disease with a therapy that is proven to slow progression, as opposed to continuing a therapy that may just benefit relapses and may even be more expensive than siponimod such as natalizumab or fingolimod.	Thank you for your comment. The choice of comparators was considered by the committee (see section 3.3 of the FAD). The views

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 clinical experts and patient/ carer representatives were considered by the Appraisal Committee when formulating its recommendations.
61	Web comment (public)	(Web commenter 9)	**Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?** I would suggest that the economic benefits of slowing disease progression should be considered in a broader sense, such as the benefits effects on employment status and need for social care.	Thank you for your comment. Comment noted. Considerations about

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 are explained in the Guide to the methods of technology appraisal section 6.2.13–6.2.19.
62	Web comment (public)	(Web comment er 9)	**Are the recommendations sound and a suitable basis for guidance to the NHS?** Siponimod is a treatment that the rest of the developed world are using to treat active secondary progressive multiple sclerosis and thus I would suggest it is wrong for Siponomod not to be used in the UK.	Thank you for your comment. Following the revised analyses submitted by the company in response to consultation,

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 committee considered siponimod to be cost-effective (see section 3.16 of the FAD), so the treatment has been recommended.
63	Web comment (public)	(Web commenter 10)	**Has all of the relevant evidence been taken into account?** No. The key issue is that there is no effective treatment for SPMS - Betaferon is 20 years old, one of the least effective DMTs and is used by only a tiny number of patients. Therefore the comparison is not valid.	Thank you for your comment. The choice of comparators was considered by the committee (see

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
				section 3.3 of the FAD).
64	Web comment (public)	(Web commenter 10)	**Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?** No. You have not factored in the huge, ongoing costs of social care and the NHS which could be alleviated through effective treatment.	Thank you for your comment. Comment noted. Considerations about cost effectiveness are explained in the Guide to the methods of technology appraisal section 6.2.13–6.2.19.
65	Web	(Web	**Are the recommendations sound and a suitable basis for guidance to the NHS?**	Thank

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 (public)	comment er 10)	No. You are denying SPMS patients the opportunity for effective treatment and leaving neurologists with no treatment options. According to your own data, there are 9000 SPMS patients in England who are being left forgotten.	you for your comment. Following the revised analyses submitted by the company in response to consultation, the committee considered siponimod to be cost-effective (see section 3.16 of the FAD), so the treatment has been

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
				recommended.
66	Web comment (public)	(Web commenter 10)	**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?** SPMS primarily affects older people. You are therefore discriminating against a group of people on the grounds of age.	Thank you for your comment. Please see the Equalities Impact Assessment for discussions about discrimination.
67	Web comment (public)	(Web commenter 11)	**Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?** No I don't believe so. See comment below.	Comment noted.
68	Web comment (public)	(Web commenter 11)	**Are the recommendations sound and a suitable basis for guidance to the NHS?** No. See below. I think they restrict treatment choice for people with MS and the clinicians caring for them.	Comment noted.
69	Web comment (public)	(Web commenter 11)	**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 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
70	Web comment (public)	(Web comment er 11)	Much is made in the recommendation that siponimod should be compared with best supportive care or interferon beta 1B. As a clinician looking after patients with MS I see an unmet need particularly in the group of patients who have been on a DMT for RRMS but may be transitioning to SPMS. It acknowledged in the appraisal that many of these patients are not diagnosed with SPMS to enable them continue with DMT. This is partly because it is very difficult to determine when the risk of relapse has passed and it is therefore safe to stop a DMT without the risk of relapse. RRMS and SPMS are a continuum of the same disease. If a person is on a DMT for RRMS we cannot be sure if they are not relapsing because of the drug or because of the natural history of the disease is to have less obviously inflammatory activity later in the disease. Patients who have disease progression on DMT may still have relapses if DMT is stopped and it is these patients especially who would potentially benefit more from Siponimod than their current DMT. The results from the EXPAND study suggest benefits to patients with progressive disease in terms of reducing brain atrophy, a potental effect on remyelination and particularly on preserving cognition. Having siponimod as an option for active SPMS patients not on treatment already is also really important. Many patients previously labelled as SPMS who have significant relapses and/or MRI activity may have their disease reclassified as RMS to be eligible for current DMTs. This is another reason why comparing against supportive care or IFN beta 1B is potentially misleading.	Thank you for your comment. The choice of comparators was considered by the committee (see section 3.3 of the FAD). Following the revised analyses submitted by the company in response to consultation, the committee

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
				considered siponimod to be cost-effective (see section 3.16 of the FAD), so the treatment has been recommended.
71	Web comment (public)	(Web comment er 12)	**Has all of the relevant evidence been taken into account?** No. The conclusion reached by NICE ignores the evidence: - Siponimod has proven to slow down disease progression significantly. - Siponimod has additional benefits in reducing cognitive impairment. - Ignores the preventative benefits of taking Siponimod early on to avoid irreversible disability setting in. Assumes interferon beta is an alternative/existing treatment for SPMS patients, although most are not prescribed interferon beta due to how aggressive/intrusion the infusions are, and difficulties in administering the treatment. The study does not consider the possible (positive) interaction with complementary treatments such as Fampyra, which can enhance the beneficial effects of Siponimod on disability management/reduction.	Thank you for your comment. The committee discussed results from the EXPAND trial and conside

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
				red siponimod to be an effective treatment compared with placebo for active SPMS (see section 3.5 of the FAD). The committee considered the evidence on siponimod's effects on cognition (see section 3.14 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
				Following the revised analyses submitted by the company in response to consultation, the committee considered siponimod to be cost-effective (see section 3.16 of the FAD), so the treatment has been recommended.

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
72	Web comment (public)	(Web commenter 12)	**Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?** No. 1) Clinical effectiveness The conclusion ignores the benefits from SPMS: - Evident /significant slowdown in disease progression. - Preventative benefits from slowing down disease progression, reversing cognitive impairments, thus maintaining independence of SPMS sufferers for longer. - Siponimod is the only available treatment for SPMS. Interferon Beta, used in the study as a comparative, is not widely prescribed as infusions are not well tolerated and very intrusive to administer. 2) Cost effectiveness: The conclusion ignores the costs of managing someone with SPMS where the disease is active and irreversible disability is progressing has not been taken into account: - Cost saving from preventative benefits of using Siponimod. NICE's approach is to wait until the MS patient is so badly advanced that they lose their independence, and become entirely dependent on the state and NHS for housing, for carers, for benefits and for healthcare; these costs are far greater on the NHS than the cost of prescribing Siponimod to slow down disease progression/disability and delay the period where SPMS sufferers are fully dependent on the state, the NHS and others. - Costs from the impact on relatives / carers of SPMS patients. Someone suffering from SPMS has a strong negative knock-on impact on their relatives, who have to provide care for their loved one, and as a result have to stop working to look after them. - The extra burden on the NHS from: o Dealing with mental health issues from relatives of SPMS patients, who have to manage the decline of their relative suffering from SPMS o Managing additional deterioration of SPMS sufferers resulting from the issues experienced in finding regular, reliable, competent carers and accommodation, which results in a lot of SPMS sufferers becoming extremely isolated, and declining physically and cognitively faster than otherwise as they are not able to get the care they need. - The cost comparison of Siponimod vs interferon beta, ignores the costs from the additional medical support needed to administer the infusions/injections, and severe side effects from interferon beta.	Thank you for your comment. The committee discussed results from the EXPAND trial and considered siponimod to be an effective treatment compared with placebo for active SPMS (see section 3.5 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
				The committee considered the evidence on siponimod's effects on cognition (see section 3.14 of the FAD). Following the revised analyses submitted by the company in response to consultation, the committee conside

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
				red siponimod to be cost-effective (see section 3.16 of the FAD), so the treatment has been recommended. Considerations about cost effectiveness are explained in the Guide to the methods of technology 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
				section 6.2.13–6.2.19.
73	Web comment (public)	(Web commenter 12)	**Are the recommendations sound and a suitable basis for guidance to the NHS?** No. The cost effectiveness argument does not take into account the additional costs to the NHS and to the state of letting SPMS patients deteriorate without treatment, and ignores the preventative benefits from early administration to SPMS patients in maintaining their independence. The cost comparison to interferon beta is not relevant as interferon beta is not widely prescribed due to how intrusive it is. The health benefits and positive effect on SPMS patients and their relatives/carers are also ignored in the conclusion reached by NICE. The trial did not consider the possible (positive) interaction with complementary treatments such as Fampyra, which can enhance the beneficial effects of Siponimod on disability management/reduction.	Thank you for your comment. Comment noted.
74	Web comment (public)	(Web commenter 12)	**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?** Yes. Discriminates SPMS patients who have been given no treatment vs those that were given access to Siponimod on the NHS before this guidance was issued (and those in US and Europe who were given access to treatment due to Siponimod having been licensed there!). This should be overruled and Siponimod should be made accessible to all SPMS patients on a discretionary basis, regardless of this guidance.	Thank you for your comment. Please see the Equalities Impact Assessment for discussions about discrimination.
75	Web comment (publi	(Web commenter 13)	**Are the recommendations sound and a suitable basis for guidance to the NHS?** Most of the drugs available for RRMS have no direct comparison for effectiveness (or are compared against Betaferon, which is much less effective than most drugs now available), but have been approved. There are so few treatment options for secondary progressive MS, I can't understand why Mayzent has been dismissed.	Thank you for your comme

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
	c)			nt. Following the revised analyses submitted by the company in response to consultation, the committee considered siponimod to be cost-effective (see section 3.16 of the FAD), so the treatment has been recommende

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
				d.
76	Web comment (public)	(Web commenter 14)	**Has all of the relevant evidence been taken into account?** No, patients with secondary progressive ms are reluctant to take beta interferon, and only 75 take it in England. There must be a reason for this	Thank you for your comment. Comment noted.
77	Web comment (public)	(Web commenter 14)	**Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?** Cost effectiveness... my father paid voluntary nhs contributions whilst he was working in Europe with a hope he would be able to get treatment to slow down the disease progression but unfortunately died from the disease at the age of 58. I have been recently diagnosed, currently receiving tysabri, have paid national insurance since the age of 16 (I am now 37), will I have treatment denied because it is more expensive than and alternative that is ineffective	Thank you for your comment. Following the revised analyses submitted by the company in response to consultation, the committee considered siponimod to 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
				cost-effective (see section 3.16 of the FAD), so the treatment has been recommended. Considerations about cost effectiveness are explained in the Guide to the methods of technology appraisal section 6.2.13–6.2.19.
78	Web	(Web	**Are the recommendations sound and a suitable basis for guidance to the NHS?**	Thank

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 (public)	comment er 14)	Not really, as only 75 people take the current treatment for SPMS. medical professionals are unsure of the efficacy of beta interferons and considering siponimod from initial trials has shown to reduce and slow disease progression It needs to be considered	you for your comment. Comment noted.
79	Web comment (public)	(Web comment er 14)	**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?** Disability and age need to be considered. I don't think it is appropriate to discount treatment because it is too expensive and that the patient is getting old	Thank you for your comment. Please see the Equalities Impact Assessment for discussions about discrimination.
80	Web comment (public)	(Web comment er 15)	The only alternative is interferon Beta 1b which some patients, such as myself, have previously used unsuccessfully. Interferon Beta 1b is a treatment I started in 2009 as a newly diagnosed person with multiple sclerosis. It caused a side effect of severe clinical depression and had no positive effect on my multiple sclerosis relapse rates.	Thank you for your comment. Comment noted.
81	Web	(Web	I think your refusal of this drug is very short sighted. There is nothing else on the market for spms that slows progression. You mention interfon but hardly	Thank

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 (public)	comment er 16)	anyone with spms gets this prescribed. It's an old drug, with no evidence of slowing down progression in spms. Medication and therapy cost thousands of pounds to treat the progressing symptoms of spms. The NHS could SAVE thousand by delaying this progression. This was the only hope for many with spms and you have taken that away without any thought of the ongoing costs of progression. If people were given this as the norm as they transition into spms you would save on all the medications and therapies they need as they progress.	you for your comment. Following the revised analyses submitted by the company in response to consultation, the committee considered siponimod to be cost-effective (see section 3.16 of the FAD), so the treatment has been

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
				recommended. Considerations about cost effectiveness are explained in the Guide to the methods of technology appraisal section 6.2.13–6.2.19.
82	Web comment (public)	(Web comment er 17)	**Has all of the relevant evidence been taken into account?** No. • Ignores the widely seen success of Siponimod for SPMS sufferers, which has been approved in the US and Europe. • Ignores the preventative benefits of starting the treatment early in slowing down disease progression and irreversible onset of disability. • Ignores the fact that there are no other treatments available for individuals with active SPMS; interferon beta-1bs are prescribed mostly for Relapsing Remitting MS, and in practice many patients are not prescribed interferon beta-1bs as they cannot tolerate the aggressive infusions of interferon beta-1b. • Does not take into account potential positive benefits of combining Siponimod (which reduces disease progression and improves cognitive abilities) with Fampyra (which improves fluidity of movements).	Thank you for your comment. The committee was aware of the lack of treatment

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
				options availabl e for people with SPMS (see section 3.1 of the FAD). The committ ee discuss ed results from the EXPAN D trial and conside red siponim od to be an effectiv e treatme nt compar ed with placebo for active

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
				SPMS (see section 3.5 of the FAD). Following the revised analyses submitted by the company in response to consultation, the committee considered siponimod to be cost-effective (see section 3.16 of the FAD), so the

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 has been recommended.
83	Web comment (public)	(Web comment er 17)	**Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?** No. 1- Clinical effectiveness • Ignores the evidence of significant slow down of disease progression and proven improvement of cognitive abilities. • Comparing Siponimod to interferon beta-1bs is irrelevant as very few SPMS sufferers are taking interferon beta-1bs, due to how invasive and aggressive the injections are on the body / poor tolerance. • Ignores the fact that interferon beta-1b interacts negatively with the supplements taken to help manage SPMS symptoms (e.g. Vitamin D), as well as the side effects of interferon beta-1b infusions have aggressive side effects (e.g. skin reactions / infections from the injections, difficulty swallowing/breathing, extreme tiredness, muscle tightness, depression, hallucinations) which cancel out the benefits from the medicine. • In addition, with COVID19, the side effects of interferon beta-1b (flu like symptoms) increase the risk that symptoms due to covid will be dismissed as a side effect of interferon beta-1b, putting SPMS patients at higher risk. 2- Cost effectiveness • The cost comparison between Siponimod and interferon beta-1b ignores the costs associated with administering interferon beta-1b (infusion requiring a team of medically trained staff, hospital/clinic space, transport to be arranged to/from hospital for SPMS patient) vs. Siponimod which is a non-invasive daily tablet that can be taken from home without medical assistance. • Costs of the state and NHS having to look after SPMS sufferers as their disability increases has not been taken into account (medical care, further interventions to manage their symptoms, benefits as they can no longer work, accommodation as they need accessible/adaptable units to live in, carers, etc.).	Thank you for your comment. The choice of comparators was considered by the committee (see section 3.3 of the FAD). The committee considered the evidence on siponimod's effects

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
				on cognition (see section 3.14 of the FAD). The committee discussed the potential benefits of siponimod being an oral treatment (see section 3.14 of the FAD). Following the revised analyses submitted by the compa

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
				ny in response to consultation, the committee considered siponimod to be cost-effective (see section 3.16 of the FAD), so the treatment has been recommended. Considerations about cost effectiveness are explained in

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 Guide to the methods of technology appraisal section 6.2.13–6.2.19.
84	Web comment (public)	(Web comment er 17)	**Are the recommendations sound and a suitable basis for guidance to the NHS?** No. • The conclusions/recommendations do not take into account key evidence of the effectiveness of the drug to delay disease progression and the preventative effects of prescribing it early, and ignores the benefits of non-intrusive treatments for individuals with SPMS and the additional costs to the NHS and the state of leaving someone with SPMS to deteriorate. • The drug is critically therapeutic to SPMS patients with evidence of active disease, and has a tangible positive impact on their life and prospects of keeping some form of independence. • The conclusions also omit the fact that the Siponimod trial included a small proportion of UK based individuals, whose supportive care will vary greatly from the countries represented in the trial, therefore the results are not meaningful for the UK population. • The conclusions do not consider the potential positive benefits of combining Siponimod (which reduces disease progression and improves cognitive abilities) with Fampyra (which improves fluidity of movements).	Thank you for your comment. Following the revised analyses submitted by the company in response to consultation, the committee considered siponim

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
				od to be cost-effective (see section 3.16 of the FAD), so the treatment has been recommended. The views of clinical experts and patient/carer representatives were considered by the Appraisal Committee when formula

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
				ting its recommendations.
85	Web comment (public)	(Web commenter 17)	**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?** Yes. • Discrimination of those with SPMS who were not offered Siponimod on the NHS prior to this guidance being published. They have the same condition, however are not given the same treatment opportunities under NHS, which is discriminatory. • This also does not take into account the individuality of SPMS and how Siponimod can be very effective on some patients. Those patients should be offered the chance to be put on the medicine, at the discretion of the medical team following each SPMS patient. • e.g. in my case (I suffer from SPMS), I am a very good respondent to Fampyra, and have a medical profile that would make me a very good respondent to Siponimod as well. I was never offered interferon beta-1bs as the infusions were deemed too intrusive / aggressive on my body. Due to an administrative error with the National Hospital for Neurology and Neurosurgery, which is taking care of me in London, I was never signed up to the Siponimod drug trial, despite having been assured multiple times that the necessary arrangements were being made, and so was taken away the chance at delaying any disease progression, despite the fact that Siponimod is susceptible to have very good results on someone like me.	Thank you for your comment. Please see the Equalities Impact Assessment for discussions about discrimination.
86	Web comment (public)	(Web commenter 18)	**Has all of the relevant evidence been taken into account?** No. Quality of life has not. This is one of very few possible DMTs for people with 2PMS. The option of an easy and quick to take tablet Vs a daily injection with known injection site issues should be taken into account.	Thank you for your comment. Quality of life was taken into account in the

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
				company's model. The committee discussed the potential benefits of siponimod being an oral treatment (see section 3.14 of the FAD).
87	Web comment (public)	(Web comment er 20)	This is just to give insight in to practice in a Large Scottish unit, and difficulties around managing secondary progressive MS. We have not used beta interferon 1b for a long time due to high incidence of NABs and modest treatment effect. We agree that MS phenotypes are a spectrum of same condition with variable combination of inflammatory and degenerative pathology. Unfortunately the Lublin modification of MS classification has not been widely adapted and treatment trials segregate patients in to relapsing and progressive and largely progressive patients being excluded from trials, until recently. It is clear that inflammatory activity occurs in progressive patients and is amenable to immunomodulatory treatment. Currently we offer patients with secondary progressive MS, one of the licensed treatments (for RRMS) or rituximab, if there is evidence of inflammatory activity based on MRI scans and/or CSF neurofilament light chain levels. This is done through peer review and Individual Patient Treatment Request scheme. Also it may be unhelpful; to re-categorise these patients in to RRMS, as it is important to recognise that these are perhaps older individuals with progressive disability, and with different treatment related risk, and may muddy natural history studies. Thus, a licensed treatment for active secondary progressive MS will be welcome development, presuming it is cost effective.	Thank you for your comment. The committee considered secondary progressive

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
				multiple sclerosis to be a continuum of relapsing–remitting multiple sclerosis (see section 3.1 of the FAD). Following the revised analyses submitted by the company in response to consultation, the committee considered

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
				siponimod to be cost-effective (see section 3.16 of the FAD), so the treatment has been recommended. The views of clinical experts and patient/carer representatives were considered by the Appraisal Committee when

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
				formulating its recommendations.
88	Web comment (professional organisation)	(Web commenter 21)	[redacted] completed a survey amongst its members. 50 subjects responded of whom 42 did not agree with NICE's decision not to recommend siponimod for treating secondary progressive multiple sclerosis with evidence of active disease (that is, relapses or imaging features of inflammatory activity) in adults.	Thank you for your comment. Following the revised analyses submitted by the company in response to consultation, the committee considered siponimod to be cost-effective (see

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
				section 3.16 of the FAD), so the treatment has been recommended.
89	Web comment (professional organisation)	(Web comment 21)	[redacted] disagrees with this statement as it doesn't represent current MS practice amongst UK neurologists who sub-specialise in MS. In our survey three-quarters (73%) of MS experts actively avoid diagnosing SPMS in patients on existing DMTs so as not to stop their DMT. Only 42% of respondents actively screen for SPMS when seeing patients on DMTs. The vast majority of neurologists (86%) are reluctant to stop DMTs in patients with SPMS on DMT because of concerns about rebound clinical and MRI disease activity and accelerated progression of the disease. Ninety percent of respondents thought it was inappropriate to stop DMTs in patients who have transitioned to becoming secondary progressive to see if they became active, i.e. potentially eligible for siponimod. Our survey implies that a large number of patients with SPMS are on existing DMTs, who may become eligible for siponimod on stopping their current DMT. However, most neurologists would be reluctant to stop the current DMT because of the potential for rebound disease activity. The [redacted] urges both Novartis and NICE to take this catch-22 situation into account when modelling the cost-effectiveness of siponimod for its licensed indication. The practice highlighted by our survey suggests that patients with early SPMS on existing DMTs, with evidence of active MS, should be eligible for switching to siponimod. These patients are not only represented by patients on interferon-beta-1b.	Thank you for your comment. The choice of comparators was considered by the committee (see section 3.3 of the FAD). The views of clinical experts and

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
				patient/ carer representatives were considered by the Appraisal Committee when formulating its recommendations.
90	Web comment (professional organisation)	(Web commenter 21)	[redacted] survey showed that 78% of neurologists don't switch patients on existing DMTs onto interferon-beta-1b. If NICE uses a network analysis it may be worth extending the analysis to other DMTs.	Thank you for your comment. The choice of comparators was considered by the committee (see section 3.3 of

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 FAD).
91	Web comment (professional organisation)	(Web commenter 21)	[redacted] urges NICE and Novartis to find a way of making siponimod cost-effectiveness for the treatment of active SPMS. Patients with SPMS feel disenfranchised and having a licensed DMT as a platform therapy for SPMS will allow the MS community to develop add-on therapies to target so called non-inflammatory mechanisms that are thought to contribute to progressive MS	Thank you for your comment. Following the revised analyses submitted by the company in response to consultation, the committee considered siponimod to be cost-effective (see section 3.16 of the FAD), so the

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 has been recommended.
92	Web comment (public)	(Web commenter 22)	**Has all of the relevant evidence been taken into account?** Yes, in the traditional sense as per NICE- primary and secondary outcome measures have been taken into account. Exploratory outcome measure like cognition has not been taken into account which is an important aspect for patients' quality of life, implications for employment i.e continued to work and staying to be employed and dependence on carers and social care. Another aspect is to be aware of the implications availability of Siponimod will bring is better connect with the correct and earlier diagnosis of SPMS which aligns with the biological evidence	Thank you for your comment. The committee considered the evidence on siponimod's effects on cognition (see section 3.14 of the FAD).
93	Web comment (public)	(Web commenter 22)	**Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?** A clinical summary is reasonable. It is fair to view the cost-effectiveness in the way the committee has when comparing to beta-interferon, though it will be difficult to do is a head-to-head comparison with beteferon as there are less than 100 patients in the whole country on betaferon. What NICE cost-effectiveness calculations do not take into consideration is indirect effect/benefit these treatments bring in order to improve the care of secondary progressive MS patients. What the availability of Siponimod can bring to the table is apart from the obvious avaiablity of disease modification treatment for the patients who are on none similar, but also an opportunity of service development in various MS clinics in the country if costed sensibly, a	Thank you for your comment. Comment 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
			phenomenon seen with the availability of other MS treatments seen in the past.	Following the revised analyses submitted by the company in response to consultation, the committee considered siponimod to be cost-effective (see section 3.16 of the FAD), so the treatment has been recommended.

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
				Considerations about cost effectiveness are explained in the Guide to the methods of technology appraisal section 6.2.13–6.2.19.
94	Web comment (public)	(Web comment er 22)	**Are the recommendations sound and a suitable basis for guidance to the NHS?** I am sure I and my patients would have liked the opportunity to have access to the treatment - clinically it works- works well on cognitive functions, works well on brain atrophy, and prevents brain volume shrinkage- within its limitations. Is there a possibility of price negotiations with the company to have a better cost-effectiveness equation? Perhaps the provision of evidence of positive effects on confirmed disability progression for a longer duration than the company may have or can collect might help the cause too.	Thank you for your comment. Following the revised analyses submitted by the compa

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
				ny in response to consultation, the committee considered siponimod to be cost-effective (see section 3.16 of the FAD), so the treatment has been recommended.
95	Web comment (public)	(Web commenter 22)	**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?** Nope	Thank you for your comment. Comment 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
96	Web comment (public)	(Web commenter 23)	**Has all of the relevant evidence been taken into account?** The effect on serum neurofilament light chain levels should be considered.	Thank you for your comment. Comment noted.
97	Web comment (public)	(Web commenter 23)	**Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?** I disagree with the clinical sections that I've already commented on.	Thank you for your comment. Comment noted.
98	Web comment (public)	(Web commenter 23)	**Are the recommendations sound and a suitable basis for guidance to the NHS?** There is an issue here as the scientific principals on which the guidance are based on are not current with the understanding of the pathophysiology of MS. Siponimod, if licensed will be prescribed by MS specialists who understand this well and therefore do not make sense.	Thank you for your comment. Comment noted.
99	Web comment (public)	(Web commenter 23)	**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?** In my opinion the decision for licensing should be based on scientific evidence, and Siponimod shows great promise in this context. By blocking at the outset, you are also in danger of blocking further drug development in this area of progressive disease. You are therefore, greatly disadvantaging this group of individuals.	Thank you for your comment. Please see the Equalities

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
				Impact Assessment for discussions about discrimination.
100	Web comment (public)	(Web comment er 23)	The diagnosis of secondary progressive MS is clinical classification of MS as relapsing-remitting (active) and secondary progressive (no longer active) has been made redundant by the discovery that there is ongoing inflammation in those previously thought to be progressive, and we may be dealing with one disease continuum rather than two distinct disease entities. Therefore, the efficacy of Siponimod in MS as a whole should be interpreted in this context. Siponimod, has anti-inflammatory properties and has been demonstrated to be efficacious in a group of individuals with ongoing inflammation that would otherwise not been eligible based on clinical classifications. The data on serum neurofilament light chain levels (a biomarker of subclinical inflammatory activity) which is reduced after Siponimod treatment backs up this hypothesis; https://multiplesclerosisnewstoday.com/2018/04/17/siponimod-reduces-levels-of-disease-activity-biomarker-in-spms-patients/. This strategy clearly makes a difference in the sub group of active progressive MS patients, delaying time to wheelchair use; https://multiplesclerosisnewstoday.com/news-posts/2019/09/06/ectrims2019-talk-158-siponimod-delays-the-time-to-wheelchair-in-patients-with-spms-results-from-the-expand-study/.	Thank you for your comment. The committee considered secondary progressive multiple sclerosis to be a continuum of relapsing–remitting multiple sclerosis (see

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
				section 3.1 of the FAD).
101	Web comment (public)	(Web comment er 23)	This is true, but in itself is a circular argument. If a treatment was available for progressive MS, then the way to monitor it would be via MRI. This is a point of neurology practice and judging treatment efficacy and shouldn't be used as arbitrator for whether or not a treatment should be made available. In my opinion, we should not bias the availability of treatment for active secondary progressive MS based on resource issues. The overall burden on resources in the long-term would in fact be small as only those demonstrating active disease initially will have repeat scans going forward. This was not a factor in the decision process for primary progressive MS with Ocrelizumab and shouldn't be for secondary progressive MS. Moreover, we shouldn't adversely disadvantage this disease category alone in the UK, particularly when it has been licensed in other parts of the world.	Thank you for your comment. The committee considered the company's approach to modelling neurology appointments and MRI scans (please see section 3.12 of the FAD). The views of clinical

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
				experts and patient/ carer representatives were considered by the Appraisal Committee when formulating its recommendations.
102	Web comment (public)	(Web comment er 24)	**Has all of the relevant evidence been taken into account?** No I suspect that the resource requirement for MRI scan has been miscalculated. All our patients in the SELKAMS area on high efficacy DMT's have yearly MRI scans. For other patients on DMT, the minimum requirement is biannual MRI. The second point is about brain atrophy and cognition which is a significant factor in job retention for many patients. It seems that the 83% reported reduction in the cortical loss has not featured in the calculation.	Thank you for your comment. The committee considered the evidence on siponimod's effects on

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
				cognition (see section 3.14 of the FAD). The committee considered the company's approach to modelling neurology appointments and MRI scans (please see section 3.12 of the FAD).
103	Web comment (public)	(Web commenter 24)	**Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?** Cannot answer without a background in statistics.	Thank you for your comment.

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 noted.
104	Web comment (public)	(Web commenter 24)	**Are the recommendations sound and a suitable basis for guidance to the NHS?** No Many patients are being treated as 'transitional MS' with high-cost DMT as clinicians are cautious about removing the RRMS label due to lack of appropriate alternatives. Making Siponimod available to NHS will fill this gap.	Thank you for your comment. Following the revised analyses submitted by the company in response to consultation, the committee considered siponimod to be cost-effective (see section 3.16 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
				so the treatment has been recommended.
105	Web comment (public)	(Web commenter 24)	**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	Thank you for your comment. Comment noted.

NICE National Institute for Health and Care Excellence

Siponimod for treating secondary progressive multiple sclerosis [ID1304]

Consultation on the appraisal consultation document – deadline for comments 5pm on Thursday 16 July 2020 email: NICE DOCS

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Novartis Pharmaceuticals UK Ltd
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

Comment number	Comments Insert each comment in a new row.

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Siponimod for treating secondary progressive multiple sclerosis [ID1304]

Consultation on the appraisal consultation document – deadline for comments 5pm on Thursday 16 July 2020 email: NICE DOCS

	Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	Novartis is disappointed by the draft recommendation from NICE not to recommend siponimod for the treatment of secondary progressive multiple sclerosis (SPMS) with active disease, especially considering NICE has recognised that treatment options for people diagnosed with SPMS with active disease are extremely limited and that "*siponimod is a promising drug that has the potential to address this unmet clinical need*."[1] Novartis is pleased that the clinical effectiveness and innovation of siponimod has been recognised by NICE, however if the initial decision remains unchanged, patients will be denied access to the first licensed oral therapy for patients with SPMS with active disease, leaving them without an effective, convenient treatment to manage their condition and help them maintain independence for longer. Novartis is grateful for the opportunity to respond to the Appraisal Consultation Document (ACD) to address the outstanding questions and would like to provide further comment and clarification on the remaining uncertainties in the appraisal. In addition to the comments provided here, a revised economic model and supporting Appendix have been provided with NICE's permission with a revised base case, taking into account the committee's preferences: • Fully incremental cost-effectiveness results, comparing siponimod with both interferon β-1b and best supportive care (BSC) • Additional cost for MRI scan for people starting siponimod • Active SPMS utilities as opposed to intention-to-treat (ITT) population utilities • Treatment discontinuation as opposed to study discontinuation • Treatment waning of 50% from Year 11 (in line with the assumptions used in NICE appraisal TA527)[2] • Scenario analyses: inclusion of an extra (3rd) neurology appointment in Year 1; Active SPMS NMA; treatment waning of 25% from Year 7, 50% from Year 10 (in line with available long-term EXPAND data); Active SPMS NMA plus treatment waning of 25% from Year 7, 50% from Year 10; weighted analyses assuming [redacted] of patients receive disease-modifying therapies (DMTs) and [redacted] receive BSC. In all scenarios of the cost-effectiveness analyses presented in the supporting appendix, including considering BSC as comparator and with the inclusion of treatment waning, [redacted]. [redacted]

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Siponimod for treating secondary progressive multiple sclerosis [ID1304]

Consultation on the appraisal consultation document – deadline for comments 5pm on Thursday 16 July 2020 email: NICE DOCS

	[redacted] The following topics are addressed within this response: • The choice of BSC as comparator • Innovation • Treatment administration costs applied in the economic model • Indirect treatment comparisons • Treatment discontinuation rates • Utility values in the economic model • Efficacy in subgroups
2	**Due to a hesitancy by clinicians to formally diagnose SPMS, many patients who would be eligible for siponimod are still diagnosed and treated as having relapsing-remitting multiple sclerosis (RRMS)** Section 3.1 of the ACD states that *"the clinical experts, patient experts, company and ERG all indicated that there is a period of transition in which people with relapsing–remitting multiple sclerosis may be suspected of having secondary progressive disease but are not formally diagnosed. This is especially the case for the population of interest in this appraisal, people with active secondary progressive disease, because they may still have relapses*." "*The patient and clinical experts also acknowledged that historically, there has been reluctance to diagnose patients with secondary progressive multiple sclerosis because there is only 1 licensed treatment, which people may already have taken. Also, disease-modifying treatments for relapsing–remitting multiple sclerosis are no longer indicated once someone is diagnosed with secondary progressive multiple sclerosis, so treatment usually stops*." The clinical expert also stated (Section 3.3 of the ACD) that "*disease-modifying therapies are sometimes used outside of their licensed indications in people with secondary progressive multiple sclerosis during the transition period from relapsing–remitting disease*." Additionally, the NHS commissioning expert statement states that *"it is thought that a proportion of patients who may be eligible for siponimod are likely to still be receiving treatment with a disease modifying treatment (DMT); this is because distinguishing between relapsing-remitting and progressive phenotypes of MS can be challenging, which, coupled with the lack of active treatments for SPMS, may result in patients remaining on DMTs as their disability progresses (transitioning from RRMS to SPMS)."* Given the uncertainty and hesitancy around diagnosing patients as having SPMS, many patients who would be eligible for treatment with siponimod are likely to still be formally diagnosed as having RRMS and therefore still receive their RRMS DMT. As acknowledged by NICE, for patients with active SPMS, the likelihood of being on treatment is much higher than in patients with non-active SPMS: A long-running multiple sclerosis (MS) real world evidence study in the UK showed that, in Q4 2019, [redacted] of

	sampled active SPMS patients were currently receiving treatment, compared with [redacted] of sampled patients with non-active SPMS.[3] Although NHS England does not commission DMTs (other than Extavia®) for patients with active SPMS, as identified by both the clinical and commissioning experts, DMTs are used in clinical practice in the undiagnosed population of patients with active SPMS. Therefore, the most appropriate comparator for siponimod should be DMTs used outside their licensed indications, as listed in the NICE scope. Novartis acknowledges that there will be a mix of patients (some currently treated whilst others are not) who would receive siponimod treatment. In order to explore this, a scenario analysis is presented in the supporting Appendix considering a weighted incremental cost-effectiveness ratio (ICER) for the analyses versus BSC and Extavia®, using the assumption that [redacted] of patients with active SPMS are receiving a DMT. This analysis conservatively assumes that all patients receiving DMT are receiving Extavia®, a lower cost DMT. The new base case analysis submitted as part of this response considers BSC as a relevant comparator, in line with the committee's preferences, however in reality, as indicated by NICE, the ERG and the patient and clinical experts, many patients eligible for siponimod are likely to be not currently diagnosed as active SPMS, therefore receiving a DMT, and may be diagnosed as having active SPMS upon siponimod availability.
3	**Siponimod is an innovative treatment offering cognitive benefits for patients in a phase of MS where there are currently limited to no treatment options** Section 3.16 of the ACD states that "*The ERG agreed that there is some evidence suggesting that siponimod benefits cognitive processing speed and that the EQ-5D may not fully capture this. The committee considered that such benefits could be important but the company had not included them in its model, nor had the company presented it with sufficient evidence of these benefits*." As noted by the committee, cognitive benefits are an important factor in treatment for patients with SPMS. It has been previously documented that cognitive impairment can have a substantial negative impact on the lives of people living with MS, affecting their quality of life, employability and social interactions.[4, 5] Clinical experts have additionally highlighted that cognition is an important part of patients' wellbeing: deterioration in cognition leads to loss of jobs, independence, and self-care ability, and impacts on social relationships, all of which have substantial impacts on mental health.[6-8] Previous studies have observed that cognition is a significant predictor of overall health-related quality of life (including both psychosocial and physical components).[9] Yet, changes in cognitive symptoms are often overlooked and underreported.[4] Cognitive impairment is one of the most disabling aspects of MS, affects 50–70% of all patients with MS and is more severe in patients with SPMS.[10] Therefore, preserving cognitive function constitutes a key aim of disease-modifying MS treatments.

Siponimod for treating secondary progressive multiple sclerosis [ID1304]

Consultation on the appraisal consultation document – deadline for comments 5pm on Thursday 16 July 2020 email: NICE DOCS

	The symbol digit modalities test (SDMT) has been suggested as the preferred test for assessing cognitive processing speed by the Multiple Sclerosis Outcome Assessments Consortium which developed its recommendations in collaboration with the Food and Drug Administration (FDA) and European Medicines Agency (EMA).[11] Among the tests of processing speed, SDMT has the strongest relationship with a brain MRI metric that is associated with cognitive performance.[12] Additionally, UK clinicians at a health technology assessment (HTA) advisory board confirmed that the SDMT is a good screening test for cognition in MS. As presented in Section B.2.6.6 of the company submission, scores on the SDMT improved in patients in the siponimod group at Month 12 and 24 in the EXPAND trial (indicating improved cognitive processing speed over time), compared with a worsening of mean scores in the placebo group. Furthermore, the proportion of patients with sustained clinically meaningful improvement (≥4 points from baseline sustained on all subsequent assessments) in SDMT was significantly greater among siponimod- versus placebo-treated patients (HR 1.28; 95% CI: 1.05, 1.55; p=0.0131).[13] The proportion of patients with a sustained clinically meaningful deterioration in SDMT was significantly less in siponimod treated patients versus placebo (HR 0.79; 95% CI: 0.65, 0.96; p=0.0157), equating to a 21% risk reduction in 6-month confirmed deterioration in SDMT of ≥4 points for siponimod compared with placebo.[13] In patients with Active SPMS, siponimod significantly reduced the risk of 6-month confirmed deterioration in SDMT of ≥4 points by 27%.[14] Additional long-term data (up to 5-years) from the open-label extension phase of the EXPAND trial , on the effect of siponimod on SDMT were presented in Section B.1.1. of Appendix B during the technical engagement response. In the open-label extension phase of the EXPAND trial, all patients received siponimod. Over this longer time period, the risk of 6-month confirmed clinically meaningful worsening in cognitive processing speed was reduced by 23% in the continuous siponimod group versus the placebo switching group, demonstrating a maintenance of effect on cognition in the long-term. The time to 6-month confirmed worsening was prolonged by 55%.[15] In recently published EXPAND data presented at the European Academy of Neurology and the American Academy of Neurology congresses earlier this year, siponimod consistently slowed cortical grey matter and thalamic atrophy. The beneficial effect was consistently observed independent of age, and disease duration, activity and severity.[16] A reduction of grey matter atrophy might positively impact long-term clinical outcomes, including disability progression and cognitive decline.[17-22] The ERG has acknowledged that the EQ-5D may not fully capture any benefits for cognitive processing speed. Cognitive benefits are also not captured in the Expanded Disability Status Scale (EDSS) or relapses within the cost-effectiveness model. As such, the cost-effectiveness results do not account for these additional, important patient benefits; the ICERs presented in this appraisal are therefore an overestimate compared with the true cost-effectiveness of siponimod. Professor Dawn Langdon, a Professor of Neuropsychology at Royal Holloway, University of London, whose work focuses mainly on cognitive aspects of multiple sclerosis, has

	provided an additional statement on the importance of cognition for patients with MS, which has been provided as an attachment to this response. Beyond cognition, siponimod represents an innovative treatment for patients for whom there are very limited treatment options available. SPMS is a typically hard-to-treat population, as demonstrated by natalizumab, one of the highly efficacious drugs licensed for RRMS, having failed in a trial in patients with SPMS.[23] None of the available DMTs in the UK have been shown to slow disability progression or cognitive impairment in a representative population of patients with SPMS.[24-27] The fact that the committee consider BSC to be the most appropriate comparator for siponimod further highlights the innovative nature of siponimod in providing a treatment to patients who are currently underserved by existing treatment options. Section 3.2 of the ACD states that "*the committee concluded that people may be formally diagnosed with secondary progressive multiple sclerosis earlier if siponimod is available*." This represents a substantial step-change in the transition and management of SPMS in the NHS, directly resulting from the availability of siponimod. Introduction of siponimod would reduce the hesitancy of formally identifying SPMS in patients and would give patients with active SPMS the option to switch to a DMT proven to be efficacious in SPMS. As an oral treatment, siponimod additionally avoids the administration requirements of infusions or injections, whilst also providing greater convenience to patients, allowing them to maintain independence for longer. As noted in the technical report for this appraisal (Section 2.4), Extavia® is "*supplied as a solvent and powder which patients (or carers) must mix in order to take. This may be difficult for people with manual dexterity, visual or cognitive difficulties, which are common in people with multiple sclerosis*." Notably, in the NICE multiple technology appraisal for beta-interferons and glatiramer acetate, the committee concluded that interferon β-1a was a cost-effective use of NHS resources for patients with RRMS, despite ICERs above the typical £30,000 threshold, by taking "*into account the equality considerations applied with respect to the group of people who will find the preparation and administration of Extavia challenging*."[2] Given the importance of benefits in cognitive outcomes for patients, Novartis would appreciate the committee's recognition of the clinically meaningful cognitive processing speed data available and innovative nature of siponimod. Siponimod addresses multiple unmet needs for patients with SPMS with active disease: siponimod helps slow declining cognitive function as well as slowing disability progression and reducing relapse rates, and as an oral therapy, offers patients an effective, convenient treatment option that allows patients to maintain their independence for longer.
4	**The economic model already captures neurology appointments for patients with active SPMS** Section 3.13 of the ACD states that "*before starting treatment, people being considered for siponimod would attend a neurology clinic and have an MRI scan that they would not normally have been offered. The clinical expert highlighted that these costs would apply only to people who had already been diagnosed with secondary progressive multiple*

sclerosis, and not to people who are transitioning from relapsing–remitting to secondary progressive disease who would generally have regular MRI scans. The committee concluded that costs associated with additional neurology visits and scans should be included in the model."

The revised model submitted to NICE as part of this response incorporates the cost of an additional MRI scan for all patients receiving siponimod. This is an overestimate of the true costs to the NHS in clinical practice for two main reasons outlined below:

- Firstly, the license wording for siponimod is for "*adult patients with SPMS with active disease evidenced by relapses **or** imaging features of inflammatory activity*." The definition of active SPMS required for initiation of siponimod is not dependent solely on observing imaging features by MRI. In the EXPAND trial, more patients in the Active SPMS subgroup had signs of relapse activity than those with MRI activity: 75.8% of patients had experienced a relapse in the previous 2 years prior to screening, compared with 44.9% of patients with at least one gadolinium (Gd)-enhancing T1 lesion at baseline.[28] The committee concluded in section 3.4 of the ACD that the Active SPMS subgroup from the EXPAND trial is representative of the NHS population of patients with active SPMS. As such, the majority of patients with active SPMS in clinical practice present with clinical features of disease activity through relapses and are eligible for treatment without the requirement for MRI evidence of disease activity.
- Secondly, section 3.2 of the ACD states that "*the committee concluded that people may be formally diagnosed with secondary progressive multiple sclerosis earlier if siponimod is available and that diagnosis would involve an MRI scan*." This acknowledged shift to earlier diagnosis for patients with SPMS suggests that many siponimod-eligible patients would be those with RRMS with signs of progression, and therefore are expected to be receiving treatment and care and receiving regular MRI scans. As such, in patients who are already observed to be transitioning to SPMS but for whom, to date, there has been a hesitancy around a formal diagnosis, an additional MRI scan would not be required as this evidence would already have been collected in previous, regular scans. Clinicians would be best placed to determine if an MRI is required or not in order to define disease activity in these patients.

The original economic model already includes two neurology appointments associated with siponimod treatment each year, including both a higher cost of a first appointment as well as a follow-up appointment in Year 1.

Patients already diagnosed with SPMS, currently receiving BSC, are less likely to have regular appointments. Although the decision to prescribe siponimod may result in a neurologist visit for these patients, this is already accounted for with the two neurologist appointments for all patients in Year 1 of the model. As requested by the committee, a scenario is presented in the supporting Appendix to include an additional (i.e. third) neurology appointment in Year 1, however this is unlikely to be reflective of true clinical practice, and the model already incorporates both first and follow-up appointments in Year 1 independent of the patient's current care (ongoing DMT treatment or BSC).

	Novartis would be grateful if the committee would re-consider whether the costs of two neurology appointments in Year one (and following years) already included in the model are sufficient, and to recognise that the assumption that an MRI for all patients is conservative, with clinicians being best placed to determine its appropriateness.
5	**The European Study Group (EU) study matching-adjusted indirect comparison (MAIC) results in a less robust and more uncertain comparison than the North American study MAIC** Section 3.8 of the ACD states that "*in the trial of interferon beta-1b by the European Study Group, known as the European trial, about 70% of people had relapses, indicating probable active disease. It considered that a matching-adjusted indirect comparison using only this trial data may provide a more reliable result than any of the indirect comparisons it had been presented with so far." "Given the uncertainties in the indirect comparisons, it would be valuable to see a matching-adjusted indirect comparison using data from the European trial.*" In the company submission, a MAIC for 3-month confirmed disability progression (CDP) was presented for the EU Study (6-month CDP data are not available from the EU Study), 6-month CDP for the North American Study, and for annualised relapse rate (ARR) a matched comparison to the average baseline characteristics of the EU and North American Studies (Section B.9.2.4 of Document B; results in Tables 41 and 42, pages 76 and 77, respectively). Novartis notes that NICE acknowledges the MAIC as an appropriate indirect treatment comparison method for this appraisal. However, although the EU study has a larger proportion of relapsing patients than the North American study, there are a number of concerns that are raised when considering the EU study for comparing treatment efficacy between siponimod and interferon β-1b which are outlined below: • The EU study population is considerably younger than both the North American and EXPAND trial populations: mean age of 41.0 years in EU study; 46.8 years in North American study; 48.0 years in the EXPAND ITT; and 46.6 years in the EXPAND Active SPMS subgroup.[28-31] Section 3.4 of the ACD states that "*the committee concluded that the baseline characteristics of the active disease subgroup in EXPAND are similar to the NHS population with active secondary progressive multiple sclerosis*." Therefore, it is questionable whether a younger population such as that seen in the EU study is reflective of the UK active SPMS population. Additionally, clinical experts at HTA advisory boards ranked age as the most influential treatment effect modifier for CDP when considering indirect treatment comparisons. • As stated, MAICs to both the EU and North American studies were presented in the company submission. However, in the comparison to the EU study, the effective sample size (N_{eff}) following matching and adjustment is reduced to less than 10% of the EXPAND ITT for 3-month CDP; N_{eff} was [redacted] for the EU study (3-month CDP), compared with [redacted] when using the North American study (6-month CDP). As noted by the ERG (section 3.7 of the ACD), reduced sample sizes increase the uncertainty. This

	substantial difference in N_{eff} means the results of the comparison with the EU study are much less robust and are subject to greater uncertainty than the results of the NA study comparison. • Additionally, 6-month CDP data are not available from the EU study. 6-month CDP is a more specific outcome measure for disability progression than 3-month CDP. Confirmation of progression at 3-months may be biased by incomplete relapse recovery. NICE has consistently favoured the use of 6-month CDP as a more appropriate measure of progression in previous MS technology appraisals.[32-35] The European Medicines Agency also favours the use of 6-month CDP to define disability progression in their guideline on clinical investigation of medicinal products for the treatment of MS.[36] In addition, in clinical practice, determining disability progression independent of relapses in unlikely to be confirmed within three months and a longer confirmation time is required.[37] • As noted by the clinical expert in Section 3.3 of the ACD response, "*healthcare professionals are uncertain about the efficacy of interferon beta-1b, so very few people with secondary progressive multiple sclerosis take it*." The EU study, in contrast to the North American study, shows that interferon β-1b is effective at reducing the time to CDP in patients with SPMS. However, given the low uptake of Extavia® in UK clinical practice, potentially reflecting clinician's uncertainty of its effectiveness, the EU study could be considered as unreflective of the true effectiveness of interferon β-1b in the active SPMS population as seen in UK clinical practice. Overall, using the EU study, 3-month CDP MAIC for comparing siponimod with interferon β-1b results in a less reliable and more uncertain comparison, with less applicability to UK clinical practice. As such, the EU study MAIC should not be considered an appropriate source of comparative efficacy for reimbursement decisions.
6	**Treatment discontinuation rates should be utilised rather than study discontinuation rates** Section 3.11 of the ACD states that "*the committee considered that treatment discontinuation rather than study discontinuation would provide a better estimate of the numbers stopping siponimod in clinical practice*" The original model applied rates of study discontinuation to model stopping treatment with siponimod for any reason. Novartis agrees with this suggested change of approach and the revised model provided in support of this response has been updated to include treatment discontinuation rates instead.
7	**Utility values in the economic model should be based on Active SPMS utility values from EXPAND** Section 3.12 of the ACD states that "*the committee was concerned that the company had derived utility values from the full EXPAND population, rather than the subgroup of people with active disease. The committee concluded that utility values from the subgroup of*

Siponimod for treating secondary progressive multiple sclerosis [ID1304]

Consultation on the appraisal consultation document – deadline for comments 5pm on Thursday 16 July 2020 email: NICE DOCS

	people with active disease from EXPAND supplemented by Orme et al. (2007) should be used in the model." Novartis agrees with this change of approach and the revised model provided in support of this response has been updated to include Active SPMS utility values from EXPAND instead of those from the ITT population. These utility values are presented alongside one another in the supporting Appendix.
8	**Efficacy in subgroups for people with Active SPMS with and without imaging features of inflammatory activity** Section 3.6 of the ACD states that "*it is possible to have active disease without any changes in imaging features, and that it is possible to progress in terms of changes on MRI without evidence of clinical progression. The committee was interested in whether siponimod is of more benefit in disease with imaging features of inflammatory activity than without, but the company did not explore this. The committee concluded that it is uncertain whether siponimod has the same effect in disease with and without imaging features of inflammatory activity*." In response to this uncertainty raised by the committee, three subgroups of the Active SPMS subgroup from the EXPAND trial are presented in the supporting Appendix, alongside the data for the Active SPMS subgroup: • **Relapsing SPMS with MRI activity** defined as patients with relapses in the two years prior to the study and with Gd-enhanced T1 lesions at baseline. • **Relapsing SPMS without MRI activity** defined as patients with relapses in the two years prior to the study but without Gd-enhanced T1 lesions at baseline. • **Non-relapsing SPMS with MRI activity** defined as patients with Gd-enhanced T1 lesions at baseline but without relapses in the two years prior to the study. As can be seen from the data shown in the Appendix, there are [redacted] between the subgroups in terms of effectiveness results (3- or 6-month CDP or ARR), nor in comparison to the overall Active SPMS population. By cutting the Active SPMS subgroup data into smaller subgroups, analyses are increasingly underpowered and unsuitable to determine differences between subgroups. Overall, siponimod is an effective treatment for all patients with active SPMS, regardless of their relapse or MRI status.

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Siponimod for treating secondary progressive multiple sclerosis [ID1304]

Consultation on the appraisal consultation document – deadline for comments 5pm on Thursday 16 July 2020 email: NICE DOCS

- 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.

Please return to: **NICE DOCS**

Siponimod for treating secondary progressive multiple sclerosis [ID1304]

Consultation on the appraisal consultation document – deadline for comments 5pm on Thursday 16 July 2020 email: NICE DOCS

References

1. National Institute for Health and Care Excellence (NICE). NICE draft guidance does not recommend siponimod for treating secondary progressive multiple sclerosis. https://www.nice.org.uk/news/article/nice-draft-guidance-does-not-recommend-siponimod-for-treating-secondary-progressive-multiple-sclerosis. Accessed 01-Jul-2020.
2. National Institute for Health and Clinical Excellence (NICE). Beta interferons and glatiramer acetate for treating multiple sclerosis. Technology appraisal guidance [TA527]. https://www.nice.org.uk/guidance/ta527. Accessed 06-Mar-2019.
3. IPSOS Multiple Sclerosis Therapy Monitor, Q4 2019 data (October – December 2019, 45 neurologists and 17 MS Nurses in the UK reporting on MS patients seen in consultation, data collected online. Participating physicians/MS Nurses were primary treaters and saw a minimum number of 15 MS patients per month). Data are © IPSOS 2020, all rights reserved.
4. Cotter J, Vithanage N, Colville S, et al. Investigating Domain-Specific Cognitive Impairment Among Patients With Multiple Sclerosis Using Touchscreen Cognitive Testing in Routine Clinical Care. Front Neurol 2018;9:331.
5. Rao SM, Leo GJ, Ellington L, et al. Cognitive dysfunction in multiple sclerosis. II. Impact on employment and social functioning. Neurology 1991;41:692-6.
6. Clemens L, Langdon D. How does cognition relate to employment in multiple sclerosis? A systematic review. Mult Scler Relat Disord 2018;26:183-191.
7. Davies F, Wood F, Brain KE, et al. The Transition to Secondary Progressive Multiple Sclerosis: An Exploratory Qualitative Study of Health Professionals' Experiences. Int J MS Care 2016;18:257-264.
8. Davies F, Edwards A, Brain K, et al. 'You are just left to get on with it': qualitative study of patient and carer experiences of the transition to secondary progressive multiple sclerosis. BMJ Open 2015;5:e007674.
9. Hoogs M, Kaur S, Smerbeck A, et al. Cognition and physical disability in predicting health-related quality of life in multiple sclerosis. Int J MS Care 2011;13:57-63.
10. Planche V, Gibelin M, Cregut D, et al. Cognitive impairment in a population-based study of patients with multiple sclerosis: differences between late relapsing-remitting, secondary progressive and primary progressive multiple sclerosis. Eur J Neurol 2016;23:282-9.
11. LaRocca NG, Hudson LD, Rudick R, et al. The MSOAC approach to developing performance outcomes to measure and monitor multiple sclerosis disability. Mult Scler 2018;24:1469-1484.
12. Benedict RH, Bruce J, Dwyer MG, et al. Diffusion-weighted imaging predicts cognitive impairment in multiple sclerosis. Mult Scler 2007;13:722-30.
13. Benedict RHB, Fox R, Tomic D, et al. Effect of Siponimod on Cognition in Patients with Secondary Progressive Multiple Sclerosis (SPMS): Phase 3 EXPAND Study Subgroup Analysis (S44.005). Presented at AAN 2019.
14. Gold R, Kappos L, Benedict RHB, et al. Siponimod Slows Physical Disability Progression and Decline in Cognitive Processing Speed in SPMS Patients with Active Disease: A Post Hoc Analysis of the EXPAND Study. Eur J Neurol 2020;27.
15. Kappos L, Giovannoni G, Gold R, et al. Long-term Efficacy and Safety of Siponimod in Patients with SPMS: EXPAND Extension Analysis Up to 5 Years. Presented at AAN 2020.
16. Vermersch P, Fox RJ, Arnold DL, et al. Effect of Siponimod on Grey Matter Atrophy in Patients with Secondary Progressive Multiple Sclerosis: Subgroup Analyses from the EXPAND Study. Eur J Neurol 2020;27.
17. Eshaghi A, Prados F, Brownlee WJ, et al. Deep gray matter volume loss drives disability worsening in multiple sclerosis. Ann Neurol 2018;83:210-222.
18. Rocca MA, Mesaros S, Pagani E, et al. Thalamic damage and long-term progression of disability in multiple sclerosis. Radiology 2010;257:463-9.
19. Schoonheim MM, Hulst HE, Brandt RB, et al. Thalamus structure and function determine severity of cognitive impairment in multiple sclerosis. Neurology 2015;84:776-83.
20. Scalfari A, Romualdi C, Nicholas RS, et al. The cortical damage, early relapses, and onset of the progressive phase in multiple sclerosis. Neurology 2018;90:e2107-e2118.
21. Fisniku LK, Chard DT, Jackson JS, et al. Gray matter atrophy is related to long-term disability in multiple sclerosis. Ann Neurol 2008;64:247-54.
22. Eijlers AJC, van Geest Q, Dekker I, et al. Predicting cognitive decline in multiple sclerosis: a 5-year follow-up study. Brain 2018;141:2605-2618.

Please return to: **NICE DOCS**

23. Kapoor R, Ho PR, Campbell N, et al. Effect of natalizumab on disease progression in secondary progressive multiple sclerosis (ASCEND): a phase 3, randomised, double-blind, placebo-controlled trial with an open-label extension. Lancet Neurol 2018;17:405-415.
24. Ghezzi A, Amato MP, Makhani N, et al. Pediatric multiple sclerosis: Conventional first-line treatment and general management. Neurology 2016;87:S97-s102.
25. Merck Europe B.V. Mavenclad Summary of Product Characteristics. https://www.ema.europa.eu/documents/product-information/mavenclad-epar-product-information_en.pdf. Accessed 21-May-2019.
26. Roche Products Limited. Ocrevus Summary of Product Characteristics. Available at: https://www.ema.europa.eu/documents/product-information/ocrevus-epar-product-information_en.pdf. Accessed 21-May-2019.
27. Shirani A, Okuda DT, Stuve O. Therapeutic Advances and Future Prospects in Progressive Forms of Multiple Sclerosis. Neurotherapeutics 2016;13:58-69.
28. Gold R, Kappos L, Bar-Or A, et al. Efficacy of Siponimod in Secondary Progressive Multiple Sclerosis Patients With Active Disease: The EXPAND Study Subgroup Analysis. Presented at ECTRIMS 2019; P750.
29. European Study Group. Placebo-controlled multicentre randomised trial of interferon beta-1b in treatment of secondary progressive multiple sclerosis. European Study Group on interferon beta-1b in secondary progressive MS. Lancet 1998;352:1491-7.
30. Kappos L, Polman C, Pozzilli C, et al. Final analysis of the European multicenter trial on IFNbeta-1b in secondary-progressive MS. Neurology 2001;57:1969-75.
31. Panitch H, Miller A, Paty D, et al. Interferon beta-1b in secondary progressive MS: results from a 3-year controlled study. Neurology 2004;63:1788-95.
32. National Institute for Health and Care Excellence (NICE). Natalizumab for the treatment of adults with highly active relapsing–remitting multiple sclerosis. Technology appraisal guidance [TA127]. https://www.nice.org.uk/guidance/ta127. Accessed 01-Jul-2020.
33. National Institute for Health and Care Excellence (NICE). Alemtuzumab for treating relapsing-remitting multiple sclerosis. Technology appraisal guidance [TA312]. https://www.nice.org.uk/guidance/ta312. Accessed 01-Jul-2020.
34. National Institute for Health and Care Excellence (NICE). Dimethyl fumarate for treating relapsing-remitting multiple sclerosis. Technology appraisal guidance [TA320]. https://www.nice.org.uk/guidance/ta320. Accessed 01-Jul-2020.
35. National Institute for Health and Care Excellence (NICE). Ocrelizumab for treating relapsing–remitting multiple sclerosis. Technology appraisal guidance [TA533]. https://www.nice.org.uk/guidance/ta533. Accessed 01-Jul-2020.
36. European Medicines Agency. Clinical investigation of medicinal products for the treatment of multiple sclerosis. https://www.ema.europa.eu/en/clinical-investigation-medicinal-products-treatment-multiple-sclerosis. Accessed 01-Jul-2020.
37. Novartis Data on File (Caseby SCL; Montgomery SM; Woodhouse FA; Kroes MK; Duddy ME). [Manuscript under development] Transition to secondary progressive multiple sclerosis: the consequences for patients and healthcare systems, a healthcare professional survey. 2019.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Siponimod for treating secondary progressive multiple sclerosis [ID1304]

Company Appraisal Consultation Document Response

Appendices

July 2020

File name	Version	Contains confidential information	Date
Company Appraisal Consultation Response Appendix	1	Yes	23rd July 2020

Contents

Tables

Figures

Abbreviations

Abbreviation	Definition
ACD	Appraisal Consultation Document
ARR	Annualised relapse rate
BSC	Best supportive care
CDP	Confirmed disability progression
CI	Confidence interval
DMT	Disease modifying therapy
EDSS	Expanded Disability Status Scale
Gd	Gadolinium
HR	Hazard ratio
ICER	Incremental cost-effectiveness ratio
ITT	Intention-to-treat
MAIC	Matching-adjusted indirect comparison
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
NMA	Network meta-analysis
PAS	Patient Access Scheme
PSA	Probabilistic sensitivity analysis
QALY	Quality-adjusted life year
SD	Standard deviation
SPMS	Secondary progressive multiple sclerosis

Appendix A: Revised cost-effectiveness analyses

A.1 Preface

In response to the Committee's preferences expressed in Section 3.15 of the Appraisal Consultation Document (ACD), new analyses are presented, with NICE's permission. These analyses use a fully incremental probabilistic framework, incorporating a new revised Patient Access Scheme (PAS) offered by Novartis, which provides siponimod at an annual price of [redacted], representing a discount of approximately [redacted] from list price, and taking into account the Committee's preferences. A number of scenarios are also presented to demonstrate the effect on the incremental cost-effectiveness ratio (ICER) of testing alternative assumptions.

The function to undertake fully incremental probabilistic analyses has been newly added in response to the Committee preferences. One methodological point to be noted is that the new fully incremental probabilistic analysis has been programmed to evaluate both intervention and comparators within each iteration of sampling probabilistic inputs, rather than to run separate iterations of input sampling for each pairwise comparison. This approach was chosen to avoid the introduction of unwanted first-order uncertainty into the multi-comparator probabilistic sensitivity analysis (PSA) when compared with the original pairwise PSA function.

A.2 Updated utility inputs

As part of the revised base case, the utility estimates have been updated to be based on EQ-5D data from the EXPAND Active secondary progressive multiple sclerosis (SPMS) subgroup as opposed to the intention-to-treat (ITT) population. The comparison of these different utility values is presented in Table 1.

Table 1: Summary of utility values for cost-effectiveness analysis

EDSS State	ITT utilities	Active SPMS utilities
0	0.825	0.825
1	0.754	0.754
2	0.660	0.660
3	[redacted]	[redacted]
4	[redacted]	[redacted]
5	[redacted]	[redacted]
6	[redacted]	[redacted]
7	[redacted]	[redacted]
8	−0.094	−0.094
9	−0.240	−0.240
10	0	0

Abbreviations: EDSS: Expanded Disability Status Scale; ITT: intention-to-treat; SPMS: secondary progressive multiple sclerosis.

A.3 Cost-effectiveness results

A.3.1. Revised company base case

The revised company base case for this appraisal includes the revised PAS and the following settings, taking into account the committee's preferences:

- Additional cost for magnetic resonance imaging (MRI) scan for people starting siponimod
- Active SPMS utilities as opposed to ITT utilities
- Treatment discontinuation as opposed to study discontinuation
- Matching-adjusted indirect comparison (MAIC) vs Extavia® using the North American study
- Treatment waning of 50% from Year 11 (in line with the assumptions used in NICE appraisal TA527)

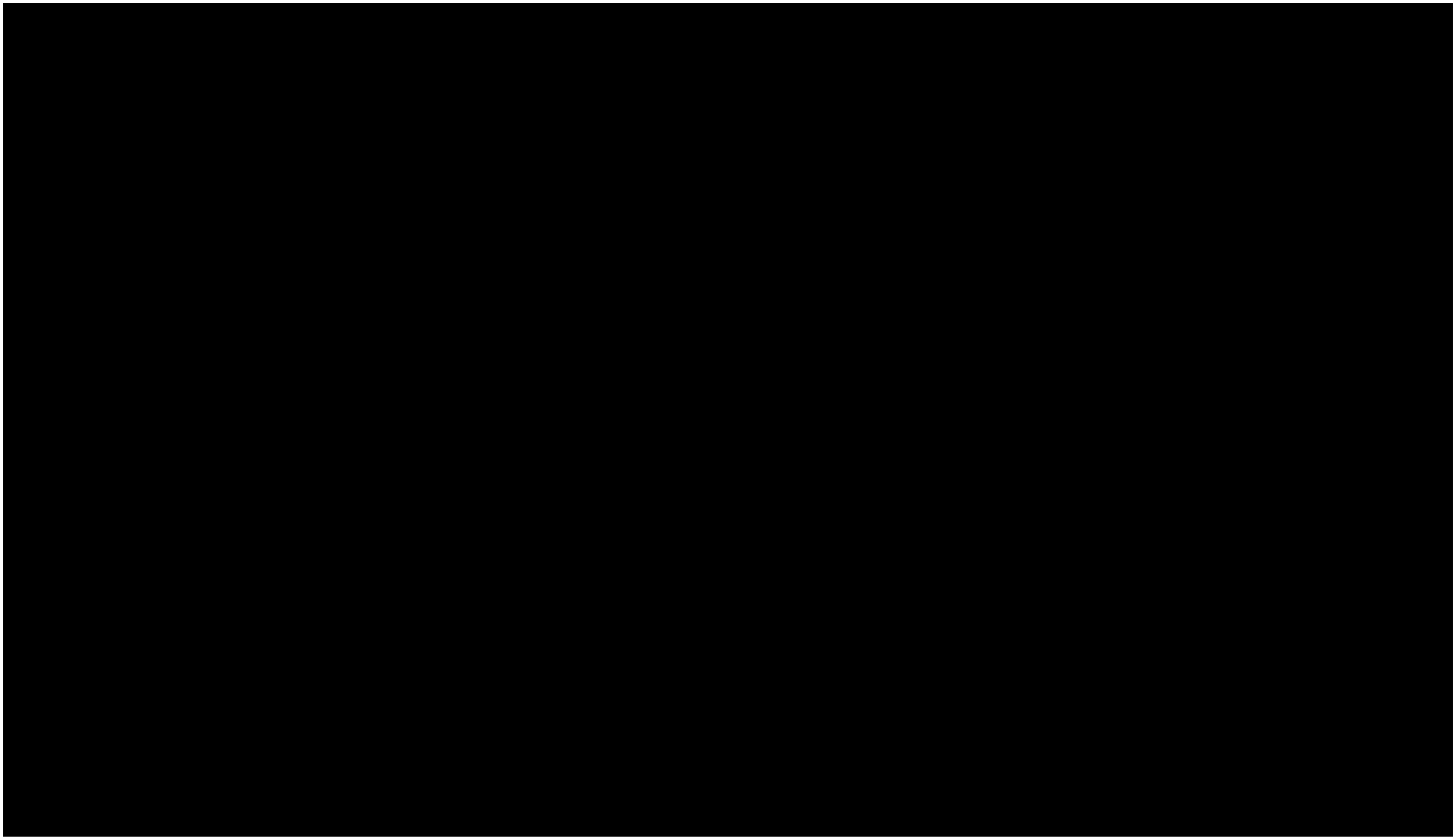
Fully incremental probabilistic results for the base case are presented in Table 2 and the cost-effectiveness acceptability curve in Figure 1. In the base case, siponimod was associated with a fully incremental probabilistic ICER of [redacted] per quality adjusted life-year (QALY) gained. The probabilities of each intervention being the most cost-effectiness treatment option at willingness to pay thresholds of £20,000 and £30,000 per QALY gained are presented in Table 3, showing siponimod to have a [redacted] probability of being the cost-effective option at the £30,000 per QALY willingness to pay threshold.

Table 2. Fully incremental average probabilistic results for the revised Novartis base case

			Step 1 (All pairwise results)			Step 2 (Fully incremental)		
DMT	**Total costs**	**Total QALYs**	**Incremental costs**	**Incremental QALYs**	**ICER**	**Incremental costs**	**Incremental QALYs**	**ICER**
BSC	[redacted]	2.75	-	-	-	-	-	-
Extavia®	[redacted]	2.85	[redacted]	0.10	[redacted]	-	-	-
Siponimod	[redacted]	3.59	[redacted]	0.73	[redacted]	[redacted]	0.84	[redacted]

Abbreviations: BSC: best supportive care; DMT: disease modifying therapy; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year.

Figure 1. Cost-effectiveness acceptability curve from the probabilistic results for the revised Novartis base case



Abbreviations: BSC: best supportive care

Table 3: Probability of cost-effectiveness

Intervention	Probability of cost-effectiveness at a £20,000 per QALY threshold	Probability of cost-effectiveness at a £30,000 per QALY threshold
Siponimod	[redacted]	[redacted]
Extavia®	[redacted]	[redacted]
BSC	[redacted]	[redacted]

Abbreviations: BSC: best supportive care; QALY: quality-adjusted life year.

A.3.2. Scenario: additional, third neurologist appointment in Year 1 for siponimod

In this scenario, as described in Comment 4 of the ACD response, an additional, third neurology appointment is added to the Year 1 costs for siponimod.

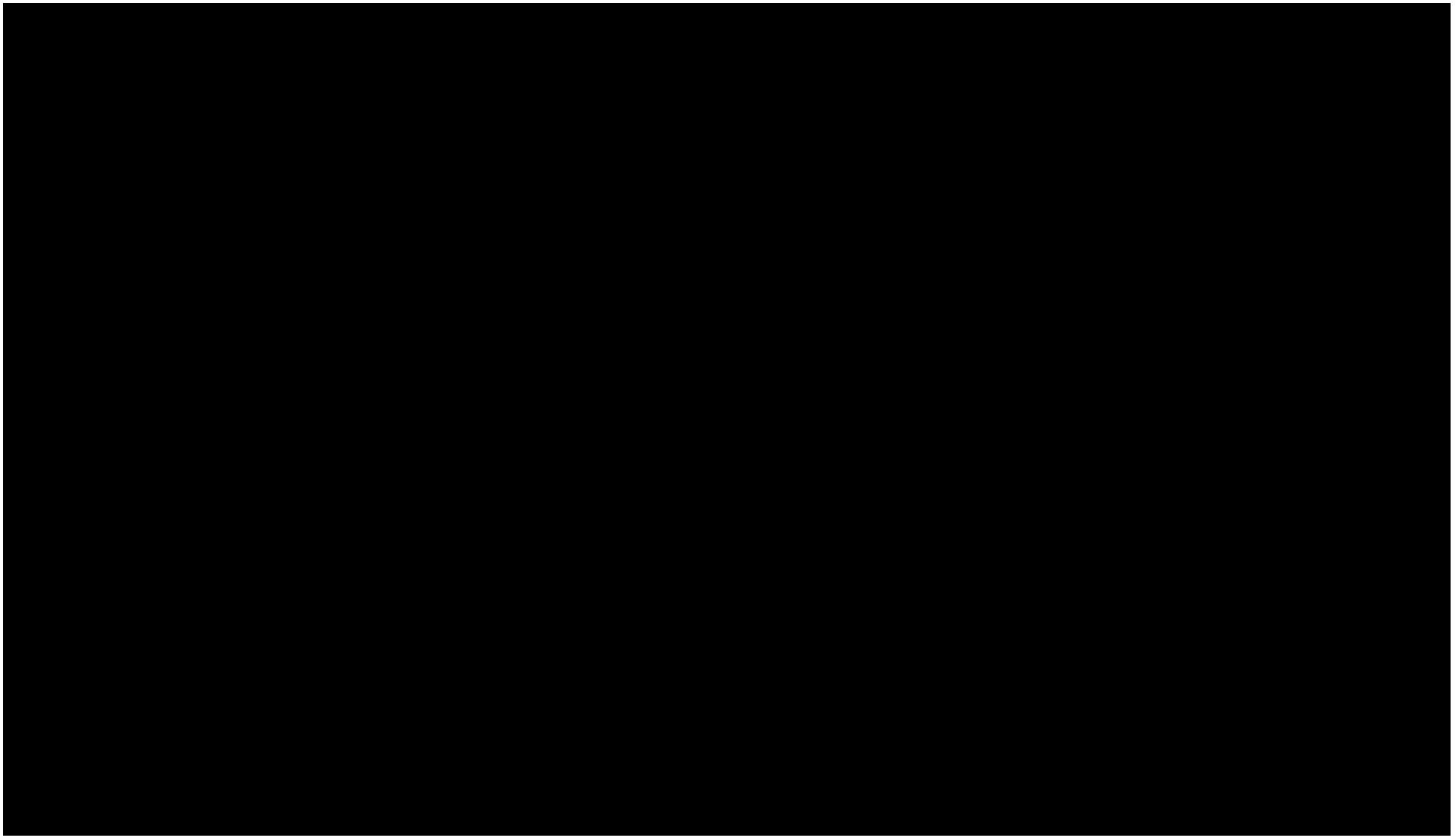
Fully incremental probabilistic results for this scenario are presented in Table 4 and the cost-effectiveness acceptability curve in Figure 2. In this scenario, siponimod was associated with a fully incremental probabilistic ICER of [redacted] per QALY gained.

Table 4. Fully incremental average probabilistic results for the revised Novartis base case with a third neurologist visit for siponimod in year 1

			Step 1 (All pairwise results)			Step 2 (Fully incremental)		
DMT	**Total costs**	**Total QALYs**	**Incremental costs**	**Incremental QALYs**	**ICER**	**Incremental costs**	**Incremental QALYs**	**ICER**
BSC	[redacted]	2.76	-	-	-	-	-	-
Extavia®	[redacted]	2.86	[redacted]	0.10	[redacted]	-	-	-
Siponimod	[redacted]	3.58	[redacted]	0.72	[redacted]	[redacted]	0.82	[redacted]

The parameter uncertainty of an additional neurology appointment is smaller than the first order (stochastic) uncertainty in the fully incremental probabilistic model; there is more variation in the base case PSA ICERs than the relatively low cost of an extra neurologist appointment. This scenario essentially shows no meaningful change from the base case.
Abbreviations: BSC: best supportive care; DMT: disease modifying therapy; ICER: incremental cost-effectiveness ratio; PSA: probabilistic sensitivity analysis; QALY: quality-adjusted life year.

Figure 2. Cost-effectiveness acceptability curve from the probabilistic results for the revised Novartis base case with a third neurologist visit for siponimod in Year 1



Abbreviations: BSC: best supportive care.

A.3.3. Scenario: active SPMS NMA

In this scenario, the Active SPMS network meta-analysis (NMA) is used in place of the MAIC. Although presented here as a scenario, Novartis maintains the preference for the MAIC in the base case as all comparisons are then based on efficacy within a population matched and adjusted for treatment effect modifiers.

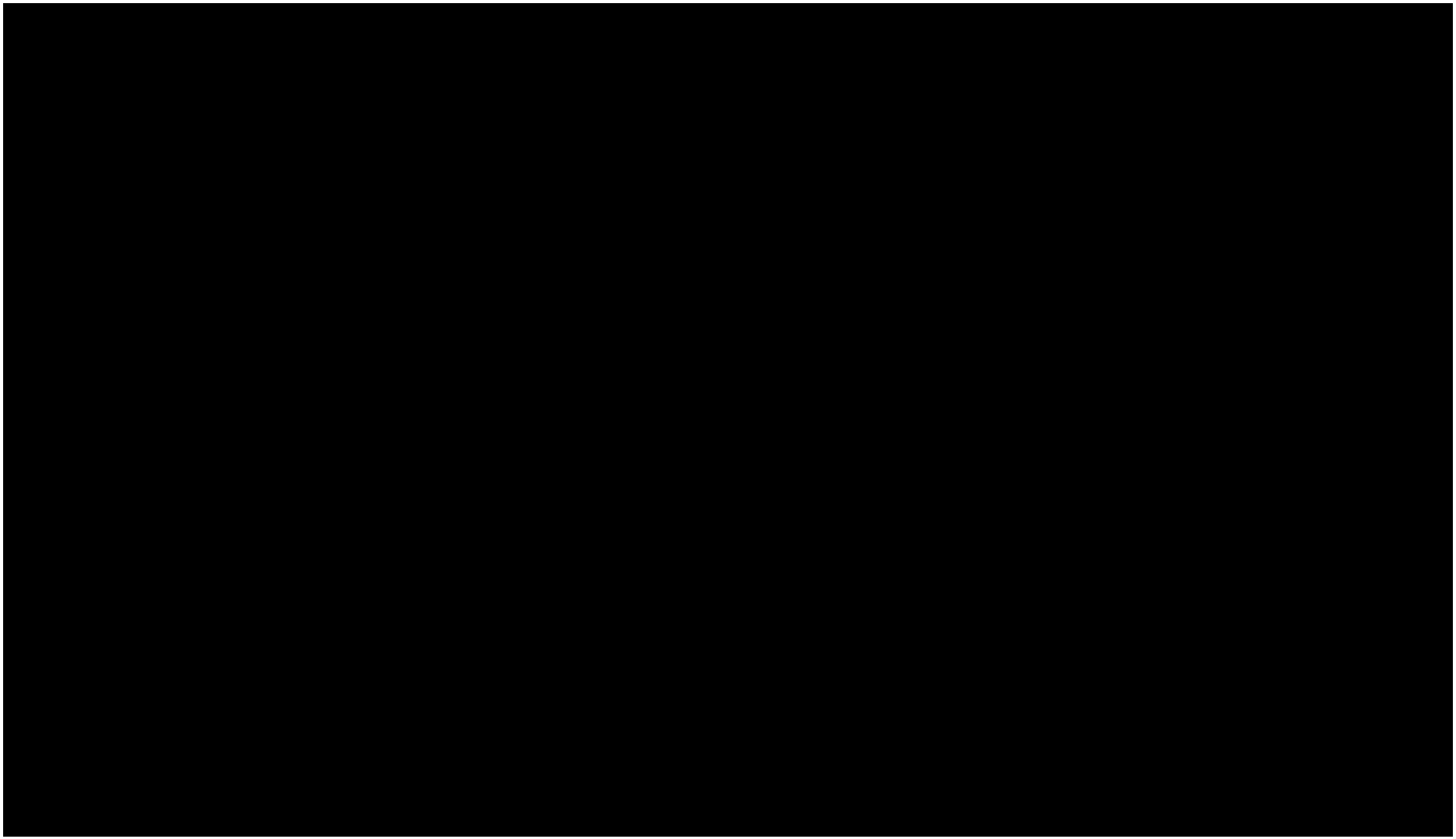
Fully incremental probabilistic results for this scenario are presented in Table 5 and the cost-effectiveness acceptability curve in Figure 3. In this scenario, [redacted], and siponimod was associated with a fully incremental probabilistic ICER of [redacted] per QALY gained.

Table 5. Fully incremental average probabilistic results for the scenario of the revised Novartis base case using the active NMA

			Step 1 (All pairwise results)			Step 2 (Fully incremental)		
DMT	**Total costs**	**Total QALYs**	**Incremental costs**	**Incremental QALYs**	**ICER**	**Incremental costs**	**Incremental QALYs**	**ICER**
BSC	[redacted]	2.78	-	-	-	-	-	-
Extavia®	[redacted]	2.87	[redacted]	0.09	[redacted]	-	-	-
Siponimod	[redacted]	3.36	[redacted]	0.49	[redacted]	[redacted]	0.57	[redacted]

Abbreviations: BSC: best supportive care; DMT: disease modifying therapy; ICER: incremental cost-effectiveness ratio; NMA: network meta-analysis; QALY: quality-adjusted life year.

Figure 3. Cost-effectiveness acceptability curve from the probabilistic results for the scenario of the revised Novartis base case using the active NMA



Abbreviations: BSC: best supportive care

A.3.4. Scenario: tapered waning from year 7

In this scenario, an alternative treatment waning assumption is explored based on a tapered waning of 25% from Year 7, followed by 50% from Year 10, based on the available long-term efficacy data from EXPAND of up to six years, submitted as part of the company's Technical Engagement response (Section B.1.1. of Appendix B).

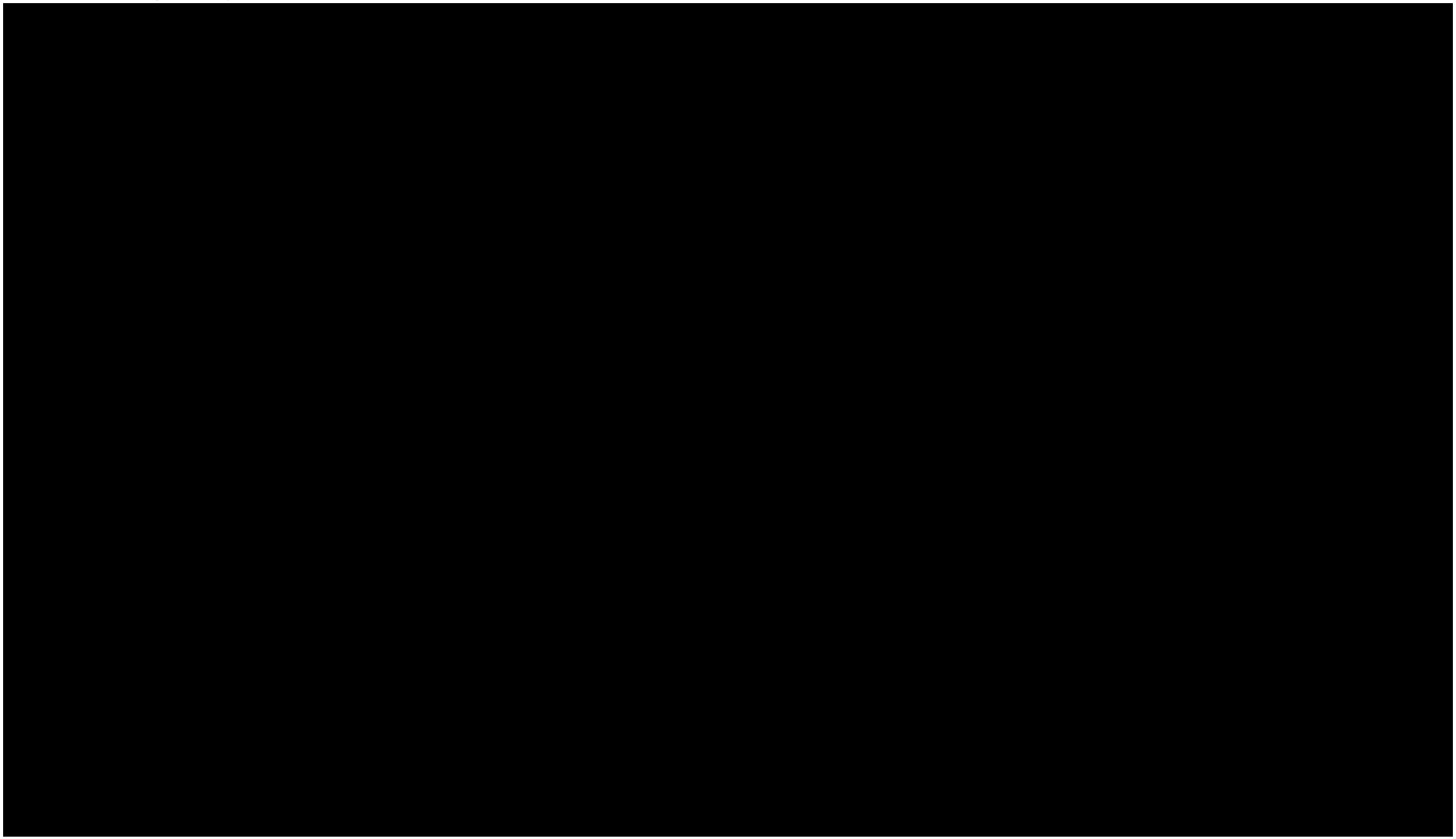
Fully incremental probabilistic results for this scenario are presented in Table 6 and the cost-effectiveness acceptability curve in Figure 4. In this scenario, siponimod was associated with a fully incremental probabilistic ICER of [redacted] per QALY gained.

Table 6. Fully incremental average probabilistic results for the scenario of the revised Novartis base case applying tapered waning from year 7

			Step 1 (All pairwise results)			Step 2 (Fully incremental)		
DMT	**Total costs**	**Total QALYs**	**Incremental costs**	**Incremental QALYs**	**ICER**	**Incremental costs**	**Incremental QALYs**	**ICER**
BSC	[redacted]	2.78	-	-	-	-	-	-
Extavia®	[redacted]	2.85	[redacted]	0.07	[redacted]	-	-	-
Siponimod	[redacted]	3.57	[redacted]	0.72	[redacted]	£11,377	0.79	[redacted]

Abbreviations: BSC: best supportive care; DMT: disease modifying therapy; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year.

Figure 4. Cost-effectiveness acceptability curve from the probabilistic results for the scenario of the revised Novartis base case applying tapered waning from year 7



Abbreviations: BSC: best supportive care

A.3.5. Scenario: active SPMS NMA and tapered waning from year 7

In this scenario, the assumptions from the scenarios presented in Section A.3.3 and A.3.4 are combined.

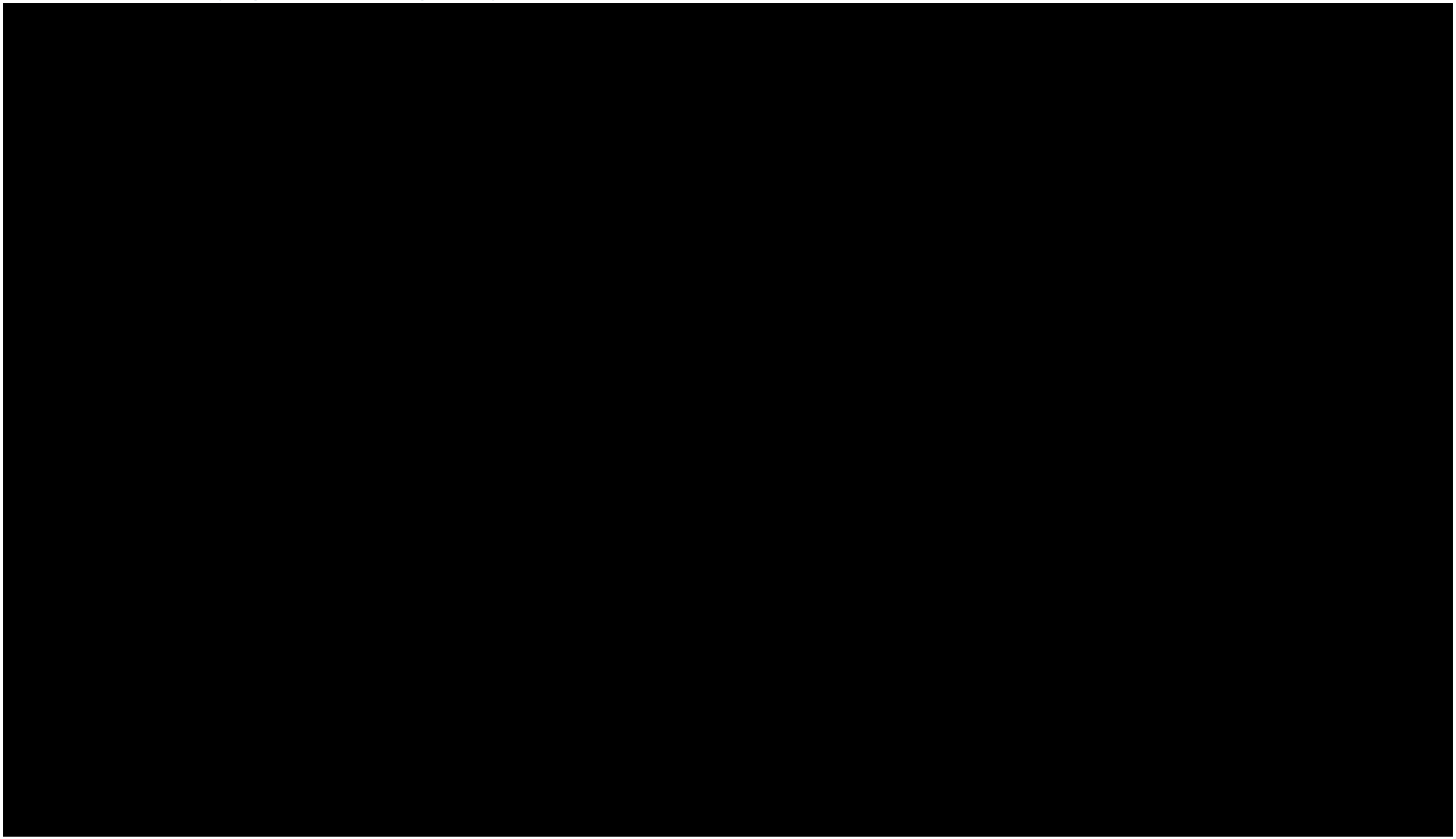
Fully incremental probabilistic results are presented in Table 7 and the cost-effectiveness acceptability curve in Figure 5. In this scenario, [redacted], and siponimod was associated with a fully incremental probabilistic ICER of [redacted] per QALY gained.

Table 7. Fully incremental average probabilistic results for the scenario of the revised Novartis base case using the active NMA and applying tapered waning from year 7

			Step 1 (All pairwise results)			Step 2 (Fully incremental)		
DMT	**Total costs**	**Total QALYs**	**Incremental costs**	**Incremental QALYs**	**ICER**	**Incremental costs**	**Incremental QALYs**	**ICER**
BSC	[redacted]	2.74	-	-	-	-	-	-
Extavia®	[redacted]	2.85	[redacted]	0.11	[redacted]	-	-	-
Siponimod	[redacted]	3.30	[redacted]	0.45	[redacted]	[redacted]	0.56	[redacted]

Abbreviations: BSC: best supportive care; DMT: disease modifying therapy; ICER: incremental cost-effectiveness ratio; NMA: network meta-analysis; QALY: quality-adjusted life year.

Figure 5. Cost-effectiveness acceptability curve from the probabilistic results for the scenario of the revised Novartis base case using the active NMA and applying tapered waning from year 7



Abbreviations: BSC: best supportive care.

A.3.6. Scenario: basket comparator

In this scenario, as described in Comment 2 of the ACD response, a basket comparator of [redacted]DMTs (using Extavia® as a proxy for all DMTs) and [redacted]best supportive care (BSC) is utilised.

Fully incremental probabilistic results for this scenario are presented in Table 8. In this scenario, siponimod was associated with a weighted, fully incremental probabilistic ICER of [redacted]per QALY gained.

Table 8. Fully incremental average probabilistic results for a basket comparison using the revised Novartis base case

DMT	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
Basket: [redacted]DMTs, [redacted]BSC	[redacted]	2.80	-	-	-
Siponimod	[redacted]	3.59	[redacted]	0.79	[redacted]

Abbreviations: BSC: best supportive care; DMT: disease modifying therapy; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year.

Appendix B: Additional subgroup analyses

B.1 Preface

Section 3.6 of the ACD states that "*it is possible to have active disease without any changes in imaging features, and that it is possible to progress in terms of changes on MRI without evidence of clinical progression. The committee was interested in whether siponimod is of more benefit in disease with imaging features of inflammatory activity than without, but the company did not explore this. The committee concluded that it is uncertain whether siponimod has the same effect in disease with and without imaging features of inflammatory activity*."

In response to this uncertainty raised by the committee, three subgroups of the Active SPMS subgroup from the EXPAND trial are presented, alongside the data for the Active SPMS subgroup:

- **Relapsing SPMS with MRI activity** defined as patients with relapses in the two years prior to the study and with gadolinium (Gd)-enhanced T1 lesions at baseline.
- **Relapsing SPMS without MRI activity** defined as patients with relapses in the two years prior to the study but without Gd-enhanced T1 lesions at baseline.
- **Non-relapsing SPMS with MRI activity** defined as patients with Gd-enhanced T1 lesions at baseline but without relapses in the two years prior to the study.

Please note that T2 lesion increase could not be included as a criterion for determining MRI activity as these data were not captured at baseline.

B.2 Baseline characteristics

Table 9: Full EXPAND baseline characteristics for subgroups

Baseline characteristic	Active SPMS		Relapsing SPMS with MRI activity		Relapsing SPMS without MRI activity		Non-relapsing SPMS with MRI activity	
	Siponimod N=516	Placebo N=263	Siponimod [redacted]	Placebo [redacted]	Siponimod [redacted]	Placebo [redacted]	Siponimod [redacted]	Placebo [redacted]
Age groups – n (%)								
18–40	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>40	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age (years)								
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Min – Max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sex – n (%)								
Female	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Male	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Duration of MS since diagnosis (years)								
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Min – Max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Duration of MS since first symptom (years)								
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Min – Max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time since conversion to SPMS (years)								
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Baseline characteristic	Active SPMS		Relapsing SPMS with MRI activity		Relapsing SPMS without MRI activity		Non-relapsing SPMS with MRI activity	
	Siponimod N=516	Placebo N=263	Siponimod [redacted]	Placebo [redacted]	Siponimod [redacted]	Placebo [redacted]	Siponimod [redacted]	Placebo [redacted]
Min – Max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of relapses in the last 2 years prior to screening								
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Min – Max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of relapses in the last 2 years prior to screening (categories) – n (%)								
None	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2–3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4–5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of relapses in the last year prior to screening								
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Min – Max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of relapses in the last year prior to screening (categories) – n (%)								
None	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2–3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4–5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time since the onset of the most recent relapse (months)								
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Min – Max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Baseline characteristic	Active SPMS		Relapsing SPMS with MRI activity		Relapsing SPMS without MRI activity		Non-relapsing SPMS with MRI activity	
	Siponimod N=516	Placebo N=263	Siponimod [redacted]	Placebo [redacted]	Siponimod [redacted]	Placebo [redacted]	Siponimod [redacted]	Placebo [redacted]
EDSS								
Mean (SD)	[redacted]							
Median	[redacted]							
Min – Max	[redacted]							
EDSS (categories) – n (%)								
<3.0	[redacted]							
3.0–4.5	[redacted]							
5.0–5.5	[redacted]							
6.0–6.5	[redacted]							
>6.5	[redacted]							
Number of Gd-enhancing T1 lesions (categories) – n (%)								
0	[redacted]							
≥1	[redacted]							
Baseline volume of T2 lesions (mm^3)								
Mean (SD)	[redacted]							
Median	[redacted]							
Min – Max	[redacted]							
Normalised brain volume (cc)								
Mean (SD)	[redacted]							
Median	[redacted]							
Min – Max	[redacted]							
MS DMTs								

Baseline characteristic	Active SPMS		Relapsing SPMS with MRI activity		Relapsing SPMS without MRI activity		Non-relapsing SPMS with MRI activity	
	Siponimod N=516	Placebo N=263	Siponimod [redacted]	Placebo [redacted]	Siponimod [redacted]	Placebo [redacted]	Siponimod [redacted]	Placebo [redacted]
Any MS DMT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

N numbers for the three subgroups total to slightly less than the N for the total Active SPMS population due to missing MRI or relapse data at baseline for some patients.
The Cox regression model includes the predictors treatment and baseline EDSS.
Abbreviations: DMT: disease-modifying therapy; EDSS: Expanded Disability Status Scale; Gd: Gadolinium; MRI: magnetic resonance imaging; MS: multiple sclerosis; SD: standard deviation; SPMS: secondary progressive multiple sclerosis.

B.3 Confirmed disability progression

B.3.1. Time to 3-month CDP

Table 10: Time to 3-month CDP based on EDSS – Cox proportional hazards model

Treatment	n/N'	(%)	Comparison: Siponimod vs Placebo		
			HR (95% CI)	% Difference	p-value
Active SPMS*					
Siponimod [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo [redacted]	[redacted]	[redacted]			
Relapsing SPMS with MRI activity					
Siponimod [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo [redacted]	[redacted]	[redacted]			
Relapsing SPMS without MRI activity					
Siponimod [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo [redacted]	[redacted]	[redacted]			
Non-relapsing SPMS with MRI activity					
Siponimod [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo [redacted]	[redacted]	[redacted]			

*Active SPMS is defined by ongoing relapses and/or MRI activity.
N=number of subjects in treatment arm and subgroup, n=number of patients with event, N'=number of patients included in the analysis, (i.e. with non-missing covariates). N numbers for the three subgroups total to slightly less than the N for the total Active SPMS population due to missing MRI or relapse data at baseline for some patients. The Cox regression model includes the predictors treatment and baseline EDSS.
Abbreviations: CDP: confirmed disability progression; CI: confidence interval; EDSS: Expanded Disability Status Scale; HR: hazard ratio; MRI: magnetic resonance imaging; SPMS: secondary progressive multiple sclerosis.

Figure 6: Active SPMS subgroup: Percentage free of 3-month CDP based on EDSS – Kaplan–Meier curves

Active SPMS is defined by ongoing relapses and/or MRI activity.
Last known date to be at risk is defined as the last EDSS assessment date in core part.
Abbreviations: CDP: confirmed disability progression; EDSS: Expanded Disability Status Scale; MRI: magnetic resonance imaging; SPMS: secondary progressive multiple sclerosis.

Figure 7: Relapsing SPMS with MRI subgroup: Percentage free of 3-month CDP based on EDSS – Kaplan–Meier curves

Last known date to be at risk is defined as the last EDSS assessment date in core part.
Abbreviations: CDP: confirmed-disability progression; EDSS: Expanded Disability Status Scale; MRI: magnetic resonance imaging; SPMS: secondary progressive multiple sclerosis.

Figure 8: Relapsing SPMS without MRI subgroup: Percentage free of 3-month CDP based on EDSS – Kaplan–Meier curves

Last known date to be at risk is defined as the last EDSS assessment date in core part.
Abbreviations: CDP: confirmed-disability progression; EDSS: Expanded Disability Status Scale; MRI: magnetic resonance imaging; SPMS: secondary progressive multiple sclerosis.

Figure 9: Non-relapsing SPMS with MRI activity: Percentage free of 3-month CDP based on EDSS – Kaplan–Meier curves

Last known date to be at risk is defined as the last EDSS assessment date in core part.
Abbreviations: CDP: confirmed-disability progression; EDSS: Expanded Disability Status Scale; MRI: magnetic resonance imaging; SPMS: secondary progressive multiple sclerosis.

B.3.2. Time to 6-month CDP

Table 11: Time to 6-month CDP based on EDSS – Cox proportional hazards model

Treatment	n/N'	(%)	Comparison: Siponimod vs Placebo		
			HR (95% CI)	% Difference	p-value
Active SPMS*					
Siponimod [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo [redacted]	[redacted]	[redacted]			
Relapsing SPMS with MRI activity					
Siponimod [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo [redacted]	[redacted]	[redacted]			
Relapsing SPMS without MRI activity					
Siponimod [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo [redacted]	[redacted]	[redacted]			
Non-relapsing SPMS with MRI activity					
Siponimod [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo [redacted]	[redacted]	[redacted]			

*Active SPMS is defined by ongoing relapses and/or MRI activity.
N=number of subjects in treatment arm and subgroup, n=number of patients with event, N'=number of patients included in the analysis, (i.e. with non-missing covariates). N numbers for the three subgroups total to slightly less than the N for the total Active SPMS population due to missing MRI or relapse data at baseline for some patients. The Cox regression model includes the predictors treatment and baseline EDSS.
Abbreviations: CDP: confirmed disability progression; CI: confidence interval; EDSS: Expanded Disability Status Scale; HR: hazard ratio; MRI: magnetic resonance imaging; SPMS: secondary progressive multiple sclerosis.

Figure 10: Active SPMS subgroup: Percentage free of 6-month CDP based on EDSS – Kaplan-Meier curves

Active SPMS is defined by ongoing relapses and/or MRI activity.
Last known date to be at risk is defined as the last EDSS assessment date in core part.
Abbreviations: CDP: confirmed disability progression; EDSS: Expanded Disability Status Scale; MRI: magnetic resonance imaging; SPMS: secondary progressive multiple sclerosis

Figure 11: Relapsing SPMS with MRI subgroup: Percentage free of 6-month CDP based on EDSS – Kaplan–Meier curves

Last known date to be at risk is defined as the last EDSS assessment date in core part.
Abbreviations: CDP: confirmed-disability progression; EDSS: Expanded Disability Status Scale; MRI: magnetic resonance imaging; SPMS: secondary progressive multiple sclerosis.

Figure 12: Relapsing SPMS without MRI subgroup: Percentage free of 6-month CDP based on EDSS – Kaplan–Meier curves

Last known date to be at risk is defined as the last EDSS assessment date in core part.
Abbreviations: CDP: confirmed-disability progression; EDSS: Expanded Disability Status Scale; MRI: magnetic resonance imaging; SPMS: secondary progressive multiple sclerosis.

Figure 13: Non-relapsing SPMS with MRI activity subgroup: Percentage free of 6-month CDP based on EDSS – Kaplan–Meier curves

Last known date to be at risk is defined as the last EDSS assessment date in core part.
Abbreviations: CDP: confirmed-disability progression; EDSS: Expanded Disability Status Scale; MRI: magnetic resonance imaging; SPMS: secondary progressive multiple sclerosis.

B.4 Relapses

B.4.1. Annualised relapse rate

Table 12: Negative binomial regression of ARR for confirmed relapses

Treatment	n/N'	Time (days)	Raw ARR	Adjusted ARR (95% CI)	Comparison: Siponimod vs Placebo		
					ARR Ratio (95% CI)	% Difference	p-value
Active SPMS							
Siponimod [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo [redacted]	[redacted]	[redacted]	[redacted]	[redacted]			
Relapsing SPMS with MRI activity							
Siponimod [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo [redacted]	[redacted]	[redacted]	[redacted]	[redacted]			
Relapsing SPMS without MRI activity							
Siponimod [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo [redacted]	[redacted]	[redacted]	[redacted]	[redacted]			
Non-relapsing SPMS with MRI activity							
Siponimod [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo [redacted]	[redacted]	[redacted]	[redacted]	[redacted]			

*Active SPMS is defined by ongoing relapses and/or MRI activity.
N=number of subjects in treatment arm and subgroup, n=overall number of relapses in the analysis period for all subjects, N'=number of patients included in the analysis, time = total number of days in the analysis period for all subjects. N numbers for the three subgroups total to slightly less than the N for the total Active SPMS population due to missing MRI or relapse data at baseline for some patients.
The negative binomial includes the predictors treatment and baseline EDSS.
Abbreviations: ARR: annualised relapse rate; CI: confidence interval; EDSS: Expanded Disability Status Scale; MRI: magnetic resonance imaging; SPMS: secondary progressive multiple sclerosis.

NICE National Institute for Health and Care Excellence

Siponimod for treating secondary progressive multiple sclerosis [ID1304]

Consultation on the appraisal consultation document – deadline for comments 5pm on Thursday 16 July 2020 email: NICE DOCS

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

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

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Siponimod for treating secondary progressive multiple sclerosis [ID1304]

Consultation on the appraisal consultation document – deadline for comments 5pm on Thursday 16 July 2020 email: NICE DOCS

	Do not paste other tables into this table, because your comments could get lost – type directly into this table.
	Over 100 people with secondary progressive MS told us why having siponimod as an available treatment option would make (or would have made) a huge difference to their lives. They raised the lack of existing effective treatment options for SPMS, the inability to inject interferons and how much easier a tablet would be to administer. We also heard from people that had been on the siponimod trial the dramatic difference it made to their functioning.
1	**Lack of treatment options is a huge problem for people with SPMS** [redacted] told us "I was diagnosed with Relapsing Remitting MS in September 2008, and my condition has deteriorated since then, eventually leading to me needing to use a wheelchair since 2013. I was eventually diagnosed with SPMS in 2014. As there were no available treatments I opted to take part in the Siponimod clinical trial. Progression seemed to immediately slow until the trial had to be put on hold for 8 months while the required approvals were provided to the study. In this time my condition deteriorated further until the trial was approved and I was allowed to get back on the drug! This drug has been essential to slow progression of my condition. I dread to think what my condition would be like if Siponimod was not available!" [redacted] told us "I was diagnosed with MS nearly 5 years ago. I only had 6 months before being told my MS was secondary progressive and there was no treatment. I have always been a very independent person, caring for my mother for twenty years until her death about a year and a half before my diagnosis. My husband has suffered from a neurological condition for almost 30 years and depends on me to do the domestic tasks around the house. Any drug that could halt the progression of the debilitating disease that MS is would be a major improvement for me and many others whose mobility and ability to function is greatly impaired." [redacted] told us "I have some I have active lesions but no treatment. I use a wheelchair outdoors and a stick and furniture support indoors. I do not want to reach the point of using a wheelchair indoors my house is old and not good for a wheelchair. My future is a dark place I try not to think about because I have no treatment." [redacted] told us "I have been using Rebif (interferon beta 1-a) for MS since 2008. I inject three times per week and, as I have been injecting for twelve years, I have developed lesions in some injection site areas. I am concerned that I will no longer have sites in which to inject. Rebif helped me to work as a [redacted] for 18 years since diagnosis (until I took early retirement last year in 2019) and it has helped me to continue driving. An oral medication would make a HUGE difference to my life. I urge NICE to promote the use of Siponimod. Jacqueline, patient expert for the NICE siponimod committee told us: "I have lived with SPMS since a diagnosis four and a half years ago following years of RRMS. An occasional wobble, wonky eye sight and the odd UTI has turned into a body limp with immobility, repeated UTIs, a mind so fretful and confused that I flare up even at the smallest of blips, and bouts of trigeminal neuralgia - a pain so shocking it ravages my very being. If that isn't a sign of active disease, I don't know what is! I can no longer walk beyond 100 metres, albeit with my walking stick as my constant companion, I fear to be replaced by the wheelchair if nothing is done. My family and friends feel so helpless as they see my once active, sociable and positive minded human being turn into a shrunken shadow of its former self. They find my situation even more frightful given that there is a well-tested and tried drug out there, already licensed across Europe, USA, Asia and Australia that could transform lives of people with active SPMS like myself."
2	**The tablet form is far preferable to injectable alternatives** [redacted] told us "I was giving myself injections of interferon for around 5 years. I would certainly have preferred a daily tablet to finding a new site to stab yourself! I have had secondary progressive MS

Siponimod for treating secondary progressive multiple sclerosis [ID1304]

Consultation on the appraisal consultation document – deadline for comments 5pm on Thursday 16 July 2020 email: NICE DOCS

	for the past 10 years and am now having to use a wheelchair". [redacted] told us "I'm losing control of my left hand and my fingers are getting crooked. I have severe and painful spasms and cramps. I can't contemplate injections so this is my only chance of medication." [redacted] told us "I have been using Rebif (interferon beta 1-a) for MS since 2008. I inject three times per week and, as I have been injecting for twelve years, I have developed lesions in some injection site areas. I am concerned that I will no longer have sites in which to inject. Rebif helped me to work as a teacher for 18 years since diagnosis (until I took early retirement last year in 2019) and it has helped me to continue driving. An oral medication would make a HUGE difference to my life." [redacted] told us "I have secondary progressive MS and have been on DMTs for 12 years, all by injection. I find the injections still painful at times and they have left my skin lumpy and unsightly. I find it difficult to find injectable sights after all these years. A tablet form would be so much easier and less stressful, hopefully my skin would recover too. Even if a tablet is too late for me it would really help those starting on therapy." [redacted] has been told by her consultant that siponimod would be an option for her and is devastated it may not be available. [redacted] told us "I suffer from secondary progressive MS and this is devastating news as Siponimod was my only hope of slowing the rate of disability which continues to deteriorate. My MS is active, I had a big relapse last November and spent a month in hospital with my MRI scans showing a lot of information. My consultant said Siponimod would be an ideal option for me. I have issues using my right hand so would find injections really difficult, I have no strength in that hand. Siponimod 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. It would also allow me to continue with part-time working to support myself for longer rather than needing to look for state help. It is very disheartening to think that finally there is a drug that will have involved much hard work and money to develop in order to help those with active progressive secondary ms which it has now been decided we are not going to be given the chance to benefit from."
3	**Siponimod was effective for people who were on the trial** [redacted] told us "I was given the chance to take part in the siponimod trial because I met the criteria and took part for over 5 years. It certainly slowed down the progression of my SPMS. I had to come off it because I was diagnosed with early stage breast cancer and I noticed a marked acceleration in my MS once I had not been taking the drug for about a year." [redacted] told us "I was on the clinical research trial for siponimod. I felt stronger and more able to push the limits of my ability without feeling utterly exhausted afterwards, although I wasn't sure if that was the placebo effect. When the trial stopped, my abilities, especially walking (I use two crutches) became harder, slower and more sluggish. They required more energy leaving me less to manage on, which lowered my mood. This was when I suspected I had been on the drug which was later confirmed by the research team. Being on siponimod had helped almost stabilise my symptoms and slowed their worsening. It had given me the ability to manage and gave me hope that my difficulties would not deteriorate too quickly. For someone with MS that hope is essential."
4	**The MS Society has heard sustained anecdotal evidence that neurologists are reluctant to diagnose SPMS because of the lack of effective treatments** While the prevalence of this practice is very difficult to measure accurately, we have heard consistently form both neurologists and people with MS that diagnoses are delayed because neurologists believe, based on evidence from their own clinical practice that patients continue to derive great benefit from these DMTs. The situation is further complicated because diagnosis of SPMS is not straightforward, as the clinical expert describes in paragraph 3.2 of the ACD.

Siponimod for treating secondary progressive multiple sclerosis [ID1304]

Consultation on the appraisal consultation document – deadline for comments 5pm on Thursday 16 July 2020 email: NICE DOCS

	However, overall our experience would support the view that having an effective treatment for active SPMS could lead to earlier diagnosis of SPMS in many cases (as noted in paragraph 3.2 of the ACD).
5	**MS Society data demonstrates that some people with SPMS are taking DMTs for relapsing remitting MS** In our My MS My Needs 3 survey in 2019, only one person with active secondary progressive MS reported using Extavia, the only DMT licensed explicitly for active SPMS, out of 936 respondents with active secondary progressive MS in the UK. The survey found that it was more common for people with SPMS to be on DMTs that are not licensed explicitly for active secondary progressive MS. For example, 33 people told us they were taking other interferons (aside from Extavia), 28 people said they were taking Tecfidera, and 23 people Tysabiri. This corroborates the assertion from the clinical expert quoted at paragraph 3.3. of the ACD that "disease-modifying therapies are sometimes used outside of their licensed indications in people with secondary progressive multiple sclerosis during the transition period from relapsing–remitting disease." This point was further corroborated by some of the people with SPMS who told us their stories as part of this consultation. Yvonne told us "I was diagnosed with relapse-remitting MS in 1998 at the age of 22. Unfortunately my condition has deteriorated over the past few years whilst still having occasional relapses, and it was confirmed in September 2019 that I have secondary progressive MS. I am concerned that no easy to-make medication is available to treat this as I have very little use of my hand. I am still taking Tecfidera for my RRMS, but live with such uncertainty of what the future holds for me and my SPMS" Overall, we feel it would be appropriate to consider the effectiveness of Siponimod against other DMTs rather than best standard of care alone.

Insert extra rows as needed

Checklist for submitting comments

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

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Siponimod for treating secondary progressive multiple sclerosis [ID1304]

Consultation on the appraisal consultation document – deadline for comments 5pm on Thursday 16 July 2020 email: NICE DOCS

- 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.

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Siponimod for treating secondary progressive multiple sclerosis [ID1304]

Consultation on the appraisal consultation document – deadline for comments 5pm on Thursday 16 July 2020 email: NICE DOCS

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

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Siponimod for treating secondary progressive multiple sclerosis [ID1304]

Consultation on the appraisal consultation document – deadline for comments 5pm on Thursday 16 July 2020 email: NICE DOCS

	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 siponimod as an NHS treatment for active secondary progressive MS. We note that the committee recognises that siponimod is a clinically effective treatment for active secondary progressive MS but has requested further analyses, reflecting their preferred assumptions. We trust that the manufacturer will provide these and respond to the technical issues raised. The difficulty in calculating cost effectiveness of MS drugs is well recognised.
2 General comment	**Huge unmet need** We wish to emphasise the huge unmet need for a treatment which will slow down progression in active secondary progressive MS (SPMS). Our announcement of NICE's initial decision to reject siponimod for SPMS was greeted by bitter disappointment from our supporters. In the absence of a cure, the biggest unmet need for people with SPMS is a treatment which can slow down or stop progression of disability. As a progressive condition, SPMS has an impact on all aspects of life – physical, emotional, social and economic. These profoundly affect not only the person diagnosed with SPMS, but their families as well. Transitioning to SPMS is a frightening and unwelcome milestone in the course of MS. The reality for people living with this condition is that this represents the point at which current treatment with disease modifying drugs is withdrawn, contact with MS specialist health professionals is significantly reduced while increasing disability and loss of independence become major concerns. Before preparing our appraisal submission to the committee, we conducted a survey to gather the views of those affected by SPMS. We received 383 responses (29 August – 17 September 2019) from people with SPMS, their families and specialist MS health professionals. Our submission to the appraisal included statistics and direct quotes from the survey, providing a powerful testimony. Their experiences provide a valuable personal perspective on living with SPMS, the impact it has on quality of life, and their perception of siponimod. Time and again respondents to our survey commented that there is currently no treatment to delay the progression of SPMS, nothing that can change the prognosis of their condition. Many people are doing all that they can to minimise the impact of SPMS, but they are all too aware that there is nothing that will slow down the progression of their disease. The benefits of slowing down progression are seen as maintaining mobility and independence for longer, allowing people to continue to work for longer, and saving costs for the NHS in the long term by preventing progression and the need for MS services and social care. These two quotes, taken from the MS Trust appraisal submission illustrate the impact on peoples' lives. • *I've had to give up my career of 10 years as a Paramedic, which I adored. I am fighting to stay at work, in an alternative role, but without treatment my working life will, undoubtedly, soon be coming to an end, which will completely crush me.* • *I am a single, widowed mother with SPMS - just 5 years ago I didn't know I had MS and now I am reliant on a wheelchair. My son is 12. The progression of my MS has not only resulted in my care needs increasing but also meant my son has required additional intervention and support.*

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Siponimod for treating secondary progressive multiple sclerosis [ID1304]

Consultation on the appraisal consultation document – deadline for comments 5pm on Thursday 16 July 2020 email: NICE DOCS

3 3.1 / 3.2 3.13	**Secondary progressive MS and MRI scans** The committee recognises that secondary progressive MS is a continuum of relapsing remitting MS and notes that diagnosis is based on signs and symptoms rather than biochemical or radiological testing. The marketing authorisation for siponimod limits its use to active disease which requires evidence of either relapses or MRI inflammatory activity; neither of these is mandatory or considered to be a more reliable indicator of active SPMS. However, the ACD then goes on to discuss the need for an MRI to confirm diagnosis of active SPMS. In practise, over a period of many months, a neurologist (and the person with MS) will notice increasing disability and interpret this as an indicator that relapsing remitting MS is transitioning to SPMS. Diagnosis of SPMS is retrospective and there are no definitive biomarkers or imaging tests that can be used to aid diagnosis; an MRI would not be use routinely to diagnose SPMS. In fact, it is quite likely that someone who is transitioning from relapsing to SPMS will not have had an MRI for some years. A relapse on top of increasing disability is sufficient to diagnose active SPMS; an MRI should not be necessary in this situation. While an MRI scan may be necessary to identify active disease in the absence of a relapse, it should not be mandatory in the presence of a relapse. Concerns about resource impact of additional MRI scans should be reviewed in the context of the introduction of ocrelizumab for primary progressive MS. Eligibility for ocrelizumab requires evidence of MS activity on an MRI scan; in practice, NHS teams have been able to exclude those who are not eligible based on other criteria, with the result that MRI screening has been minimised and the introduction of this treatment has not had as great an impact on services as was anticipated.
4 3.3	**Comparators – interferon beta 1b** It is widely acknowledged by clinical experts and NHS commissioners that because there are no treatments for SPMS, clinicians delay diagnosis and continue to prescribe all of the disease modifying drugs beyond the transition from relapsing remitting to secondary progressive MS. A survey of UK MS neurologists and nurses revealed that the most common reason for reluctance to diagnose SPMS was withdrawal of disease modifying drugs[1]. It is also acknowledged that interferon beta-1b, the only treatment licensed for SPMS with active disease, is taken by just 75 people in England. Prescribing of interferon beta 1b (Extavia) is very low, especially in people with active secondary progressive MS; it is self-injected and is supplied as solvent and powder which must be made up each time it is taken. The Patient Information Leaflet for Extavia details the seventeen step instructions for doing this. People with manual dexterity, visual or cognitive difficulties, all of which are common problems in secondary progressive MS, will find this very difficult, if not impossible, to do. The conclusion of the committee that "some people with active secondary progressive multiple sclerosis take interferon beta-1b but most people have no disease-modifying treatment" may reflect policy but it certainly does not reflect practise. On the contrary, people with active secondary progressive would be highly likely to be taking one of the disease modifying drugs. For an accurate picture of the current cost to the NHS of treating active secondary progressive MS, this appraisal must recognise that established clinical management includes all of the disease modifying drugs at least up until an established EDSS 7, even though this is outside of marketing

[1] Duddy M et al. Diagnosis of Secondary Progressive Multiple Sclerosis in UK Centres: Results from the Spectrum Study. Poster presented at MS Trust Conference 2019. Available at https://www.mstrust.org.uk/sites/default/files/ms_conference_posters_2019_Duddy_M_FINAL.pdf.

	authorisation. As a minimum, a blended comparator of disease modifying drugs based on UK market share should be used to properly reflect the true cost to the NHS of current treatments used for active SPMS. Failure to approve siponimod for NHS treatment of active SPMS will result in continued use of disease modifying drugs which have not been demonstrated to be effective against progression in SPMS and represent a significant cost to the NHS.
5 3.3	**Comparators - best supportive care** The committee concludes that best supportive care is a relevant comparator. We do not believe this is correct, in reality the population most likely to be eligible for siponimod will be taking one of the disease modifying drugs. Best supportive care was initially included in the draft scope but subsequently removed from the final scope in response to stakeholder comments. The final scope included established clinical management, including disease modifying therapies used outside their marketing authorisation. As noted in comment 4 above, a blended comparator of disease modifying drugs based on UK market share should be used to properly reflect the true cost to the NHS of current treatments used for active SPMS. Best supportive care is not defined in the ACD, nor are costs provided, so it is impossible for us to comment on the composition and level of NHS services that is assumed to be available across England and Wales. There is currently no research or professional consensus on what best supportive care for SPMS might be or how much it might cost. The concept of best supportive care is idealistic. It is unrealistic to assume that all people with MS have access to high quality care that fully meets their needs. The reality is that people with MS often have very limited access to services. It is clear from the data collected in our survey that people with SPMS have a high level of need for NHS care. Given the wide range of symptoms that people with SPMS may experience, it is important that there is access to a range of therapies delivered by skilled health professionals, competent in MS care. In reality, access to NHS and social care interventions such as physiotherapy or neurorehabilitation are limited, sporadic or even non-existent. Calculation of the cost of providing best supportive care cannot assume an ideal situation where these services are readily available. We are aware that people with SPMS are often 'discharged' from MS services, either due to a perception that there is no treatment available for SPMS or due to limitation in service capacity. Overwhelmingly, the message that people receive from MS health professionals is that there is no treatment available for SPMS. The quality of and access to care is highly dependent on where an individual lives. An MS Society report found that 40 per cent of MS specialist centres failed to offer people with MS a truly multi-disciplinary clinic[2]. This was also reflected in the Royal College of Physicians national audit of services for people with MS which found only 43% of people said they knew they had access to specialist neuro rehabilitation and 57% said that they had access to specialist MS physiotherapists[3].

[2] MS Society, MS 2015 Vision, (2011)
[3] RCP and MS Trust, National Audit of services for people with Multiple (2011)

Siponimod for treating secondary progressive multiple sclerosis [ID1304]

Consultation on the appraisal consultation document – deadline for comments 5pm on Thursday 16 July 2020 email: NICE DOCS

	In 2011 the National Audit Office report for services for people with neurological conditions found that the case loads of MS nurses varied extensively in each Strategic Health Authority[4]. A survey[5] conducted by the MS Trust in 2016 found that on average, people with progressive MS are seeing MS specialists much less often than people with relapsing MS. People with SPMS and their families go to great lengths to remain active and independent and do whatever they can to stay in work. This often involves paying privately for treatments with limited availability through the NHS, such as Sativex, physiotherapy or chiropody, or treatments which are not available at all, such as Fampyra. This further demonstrates that, on the ground, "best supportive care" does not meet the needs of people with SPMS. We do not believe that modelling accurately reflects the true experience of NHS treatment for many people with SPMS and that, for some people, progression is more rapid due to limited availability of care.
6 3.16	**Innovation** The committee questions the innovative nature of siponimod. There are a number of aspects of siponimod treatment which have not been captured within the cost effectiveness calculations. Siponimod is the first oral drug to show a reduction in disability progression in active secondary progressive MS. An effective treatment for people with secondary progressive MS would be truly life changing. The availability of a treatment for secondary progressive MS will provide hope for people diagnosed with this type of MS and will lead to a more optimistic and constructive interaction with neurologists and improved quality of life not captured by clinical trial EQ5D measures. Siponimod is taken orally once daily at home, a route of administration which is generally preferred by patients, leads to good adherence and has low impact on NHS services. It is also anticipated that monitoring requirements (for example blood and urine tests) for siponimod will be moderate with low impact on NHS services. In addition to its effect on disability progression, siponimod has been shown to improve cognitive performance as measured by the Symbol Digit Modalities Test. Slower performances on SDMT correlate well with activities of daily living and employment status; impaired performance on SDMT in people with MS has also been linked to decline in financial income, independently of physical disability. Our survey asked people with SPMS how the condition affected them physically; out of 235 responses to this question, 56% reported cognitive problems. An improvement in cognitive function would offer a significant benefit to people with active secondary progressive MS, allowing them to remain in work for longer and maintain family and social relationships for longer.
7	**Conclusion** The MS Trust wishes to state in the strongest possible terms the potential benefits of siponimod for active SPMS in terms of meeting the huge unmet need, delaying disease progression, and the impact on the daily lives of this group of people. Although people do all that they can to minimise the impact SPMS has on their lives, they are all too aware that there is nothing that will slow down the progression of their disease. As well as the long-term impact on mobility, work and independence, the psychological impact of a future with SPMS should not be underestimated. Our research has highlighted that the message people received from MS health professionals is that there is no treatment available for SPMS, which adds to that burden.

[4] National Audit Office. Services for people with neurological conditions (HC 1586). TSO, 2011
[5] MS Trust. Is MS care fair? MS Trust; 2016

NICE National Institute for Health and Care Excellence

Siponimod for treating secondary progressive multiple sclerosis [ID1304]

Consultation on the appraisal consultation document – deadline for comments 5pm on Thursday 16 July 2020 email: NICE DOCS

	The introduction of disease modifying drugs for relapsing remitting MS has been the catalyst for significant improvements in MS services for people with relapsing MS. The introduction of a treatment for active SPMS would similarly result in a greater focus on services for progressive MS and a more pro-active approach to managing SPMS which would ultimately benefit a much wider group of people than just those who might be eligible for siponimod.

Insert extra rows as needed

Checklist for submitting comments

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

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Siponimod for treating secondary progressive multiple sclerosis [ID1304]

Consultation on the appraisal consultation document – deadline for comments 5pm on Thursday 16 July 2020 email: NICE DOCS

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

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

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Siponimod for treating secondary progressive multiple sclerosis [ID1304]

Consultation on the appraisal consultation document – deadline for comments 5pm on Thursday 16 July 2020 email: NICE DOCS

	Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	We are grateful for the opportunity to comments on the appraisal consultation document. Siponimod for treating secondary progressive multiple sclerosis. Our response is as follows:- Has all of the relevant evidence been taken into account? Yes Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? No Whilst we agree that not many patients with active SPMS will be on a beta-interferon, there will be some. Most will still be on a higher potency treatment which will carry a greater total cost (to include infusions and monitoring). There will be the additional journeys to the hospital for both patients and their cares which, at this moment in time, we should be making great efforts to limit. It is appreciated that the use of these higher potency therapies may not strictly be within the guidance, however it reflects real world practice and therefore cost calculations should accommodate it. All of these patients will already be under the care of a specialist and be undergoing regular MRI surveillance. Are the recommendations sound and a suitable basis for guidance to the NHS? No For reasons above. 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
2	
3	
4	
5	
6	

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about 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.

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Siponimod for treating secondary progressive multiple sclerosis [ID1304]

Consultation on the appraisal consultation document – deadline for comments 5pm on Thursday 16 July 2020 email: NICE DOCS

- 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.
- 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.

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Siponimod for treating secondary progressive multiple sclerosis [ID1304]

Consultation on the appraisal consultation document – deadline for comments 5pm on Thursday 16 July 2020 email: NICE DOCS

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

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Siponimod for treating secondary progressive multiple sclerosis [ID1304]

Consultation on the appraisal consultation document – deadline for comments 5pm on Thursday 16 July 2020 email: NICE DOCS

	Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	We are concerned that most HCPs are reluctant to diagnosis SPMS due to the withdrawal of treatment or staying on sub optimal treatment
2	We are concerned comparing Siponimod to beta interferon is counter-productive – they not comparable
3	We are concerned that the guidance contradicts the Brain Health initiative (protecting the brain and slowing progression and brain atrophy
4	We are concerned that the report fails to recognise the impact and evidence of siponimod preventing the worsening of cognition which ensures people remain independent and in employment longer
5	
6	

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about 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.
- 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.

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Siponimod for treating secondary progressive multiple sclerosis [ID1304]

Consultation on the appraisal consultation document – deadline for comments 5pm on Thursday 16 July 2020 email: NICE DOCS

Please return to: **NICE DOCS**

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:	
I am at a worse loss now if that could ever be thought possible in my SPMS daily nightmare. Since progressing from RR I have been offered and so not received any treatment, care or consideration, I feel completely ignored and useless with little impetus to continue with this existence, it's no longer a life, all I achieved has been rendered useless. Thanks for evermore nothingness	

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	
Has all of the relevant evidence been taken into account? One of the points about Siponimod was that it would have an impact on the NHS workforce mainly in relation to MRI increase scanning that would be required for seeking eligibility for this medication, however this should not be a prerequisite for this drug as you rightly point out that it would lead to increased scanning but this scanning would be potentially unnecessary. Many people have clear clinical relapses that do not need a scan but due to rigors of having to prove that a medication should be given Neurologists are scanning far more than is strictly necessary. MRI's don always pick up relapses and do not always show cognitive relapses. A way that the NHS would be impacted by Siponimod would be to allow people with SPMS a medication for their condition that they have not truly had before, interferon beta in the form of Extavia is a very poor medication for them as it is given on alternate days and causes fatigue and flu like symptoms and is a poor devise for administration. Why would people who have high levels of fatigue and potentially struggling to hold onto their careers want to administer a medication with these side effects. We have no one on this medication in my clinic as it is so poorly tolerated. However the people on the clinical trial we have on Siponimod have a few side effects at the start of the medication and are happy to continue on it as it has no continuing side effects. Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence? Probably but I do think comparing siponimod with Extavia is a poor comparison as the side effects on people with MS do not allow it to be used frequently. Comparing any drug with no available medication is bound to be expensive.	

My understanind is that siponimod has a good effect on cognitionbut this is not mentioned.

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

I do understand that cost has to be considered in the NHS it is essential, but 2 of the people on Siponimod on our clinical trials have been able to increase their hours of work and are therefore contributing to society which I cannot see that has been included in the recommendations.
The guidance is not suitable for the NHS as when people with MS realize that this medication has been turned down for use we will be inundated by calls asking us why they cannot have this medication. This is a hidden impact of the decision to reject this drug but has a huge impact on my workload. Obviously if it is recommended tis would require extra clinic time which in turn would have a big impact on my service but that would be accommodated as fingolimod was. That medication is one that is well tolerated and can be supported within the NHS well.

- 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?

More women are affected with SPMS than men and more will have hidden disabilities which may be seen as not being so important and therefore not worth doing anything about, but siponimod can and I have seen it slow down the progression of MS in my small number of people I have on this medication and I would recommend people with active SPMS and who are still able to walk with bilateral support to put themselves forward for testing. If it is turned down it could be seen as being sexist and discriminatory to people with disabilities.

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	

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

No

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

No

Recommendations

As you have recognised, take up of Interferon beta-1b (IB1b) is low. I think it is important to note that IB1b is not suitable for many patients with secondary progressive MS where cognitive function is affected, and it is in turn not offered. Making a recommendation on the lack of comparative study with existing treatment options ignores the needs of many. Furthermore, were a comparative study carried

out, it is likely it would not reflect the wide spectrum of MS patients due to the limited take up.

This is not always offered, I know of a patient that after returning from living abroad as a diplomatic spouse, was not seen by a consultant for 12 years. This was only organised when symptoms were noticeably declining through GP referral (which took a further 2 years). They have now been diagnosed with SPMS and never had the opportunity to try other therapies before this stage.

It is heartbreaking that this is a decision based on economic cost-effectiveness rather than quality of life of patients. Committee papers themselves state "Siponimod offers patients with SPMS, clinicians, and the NHS a step-change in therapy, addressing for the first time their need for a DMT by offering them a treatment with proven efficacy on disability progression in SPMS." (B. 2. 13. 3)

committee-discussion

I have considered the evidence submitted, and one detail from the MS Society that I wanted to raise. The answer to Q10 (disadvantages of the technology) tells of a patient that struggles with blister packaging and it is noted that patients with cognitive problems, such as executive dysfunction, may struggle to administer a daily medication. One successful mitigation to both of these arguments is the availability of 'Medi-packs'.

Their answer to Q15 (bullet 3) also adds weight that the recommendation on cost-effectiveness may not be robust.

Surely the expert research outcomes should be given more weight than the committee's preferences. When it comes to denying treatment for many who would otherwise have an improved quality of life.

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	

Has all of the relevant evidence been taken into account?

No ... the number of people affected with SPMS is incorrectly stated.

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

No, the benefits of delaying disease progression are not considered in this report.

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

No. The recommendations are requesting further trials when there is sufficient evidence to approve this drug as there is evidence of a delay in disease progression being achieved.

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

Recommendation 1

This recommendation should be urgently amended.

siponimod had a (?) probability of being the most cost-effective option at a willingness-to-pay threshold of £30,000/QALY.

75,000 people are (or will be) affected by SPMS. This population need hope at a time when their future hopes are being ripped away as they progress in their disease. Delaying disease progression is of the utmost importance and Siponimod offers this potential.

Here are comments on the Committee discussion:

Subsection 3.3
Where has the estimate of 9000 people with SPMS come from? There is no accurate data but if I am surmising from the 'forgotten many' report, the true numbers could be:
130k people diagnosed with MS in UK.
Of these 85% are RRMS from which 2/3 are estimated to develop SPMS.
My maths indicate 73k people might transition to SPMS in the UK.

Subsection 3.5
Confirms that Siponimod is beneficial Compared to placebo in active secondary progressive population … So it is of benefit in cases of active disease.

Subsection 3.6
The interest in imaging features is irrelevant to the life of a person with MS. The EDSS is the only way to assess the impacts. Therefore this consideration might be interesting to a clinician, but surely that is not the purpose of a disease modifying therapy?
The individual writing this comment has a profuse spread of old disease activity on her MRI, but doesn't show a EDSS progression. Please do not insist on seeing imaging activity when making a decision on drug efficacy.

Subsection 3.7
"The committee concluded that there were substantial uncertainties associated with all of the indirect comparisons." Is irrelevant when all data sets favour Siponomid over Betaferon.

Subsection 3.8
However in the absence of like for like comparison, the beneficial results in Europe prove a case to make Siponimod available in the UK. The fact that EMA and FDA have approved indicate there is enough data to decide now.
You do realise that every day counts for a person with MS?

Subsection 3.11

This is more useful for the future once people with MS are using Siponimod. It does not affect a decision on whether the drug has benefits sufficient to justify approval.

Subsection 3.13
In the recently published “The Forgotten Many” (June 2020) the paper refers to the costs associated with MS correlating with disease severity. Therefore, approval of a drug that delays the progression of disease severity (such as Siponimod) would reduce the costs per patient. This would more than offset the additional neurology visits and a once per year MRI scan.

Subsection 3.14
The waning effect for a different drug which is used in the relapsing phase of disease is not comparable to the waning in a drug which is used for people with SPMS. The disease course is on a different trajectory at this point. Therefore it might be useful to model the incomparable data, but it is not necessary within the scope of approval for this drug which is to be marketed to a different population.

Subsection 3.15
Most of the preferences in this section are not relevant to making a decision because, as pointed out in comments on the previously subsections, these factors are not necessary to reach an informed decision. The decision paper states “include the costs of neurology appointments and MRI scans for people starting siponimod” but this needs to also include the benefits of slower disease progression and the resultant impact on lower impact on GPs, hospital admissions, care facilities, DSS benefits. (Or maybe delete this preference from the document?).

committee-discussion

Interferon beta-1b and best supportive care are the relevant comparators

Where has the estimate of 9000 people with SPMS come from? There is no accurate data but if I am surmising from the ‘forgotten many’ report, the true numbers could be:
130k people diagnosed with MS in UK.
Of these 85% are RRMS from which 2/3 are estimated to develop SPMS.
My maths indicate 73k people might transition to SPMS in the UK.

A matching-adjusted indirect comparison using data from the European trial may provide the best estimate of siponimod compared with interferon beta-1b

However in the absence of like for like comparison, the beneficial results in Europe prove a case to make Siponimod available in the UK.

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	

Comments on the ACD:
Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence? Summary of cost effectiveness is not reasonable as it compares siponimod to a treatment that is not widely used and does not consider the wider economic case of treatment committee-discussion No analyses reflect the committee's preferred assumptions The committee are comparing siponimod to beta interferon despite noting that beta interferon is rarely prescribed for secondary progressive MS. Instead the committee should compare siponimod to no treatment taking into account the economic cost of increased disability to society proposed-date-for-review-of-guidance Siponimod is currently subject to an ongoing open label extension. This trial is likely to gather evidence that may address the gaps identified by the committee. The review date should be bought forward to the anticipated date when further information will be available

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	
Has all of the relevant evidence been taken into account? Impact in cognitive function not considered enough Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence? Unrealistic to think that active comparator is no DMT or Beta 1b 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 committee-discussion the majority of people being considered for siponimoid would be having regular MRI's due to the requirements of other DMT's. Interferon beta-1b and best supportive care are the relevant comparators	

It is my opinion that in the real world many SPMS patient with EDSS less than 6.5 will be continuing on a DMT and therefore the active comparator to siponimoid in terms of cost is not 'no treatment'. Diagnosing someone with SPMS is not clear cut and often requires observation over many months or even years. Due to this difficulty in diagnosis and the possibility of a transition period where relapses are still possible, patients and health care professionals often choose to be caution in stopping DMT and the patient remains on when it is likely they are no longer RRMS. Another current factor is a patients reluctant to stop a DMT when their are no other options for SPMS. In my experience Interferon beta-1b is not a treatment prescribed for SPMS.

The company suggests that its modelling does not capture additional benefits, but has not presented this evidence to the committee

Comment on section: The company suggests that its modelling does not capture additional benefits, but has not presented this evidence to the committeeThe company suggests that its modelling does not capture additional benefits, but has not presented this evidence to the committee

Cognitive changes in MS are very common and often one of the symptoms that patients reports is the most difficult and frustrating to live with. It is often cognitive decline that will lead to the decision to stop working. In the appraisal there was no consideration to the impact siponimoid could have on slowing this cognitive decline. The clinical trails had a possible effect on brain volume loss and cognitive processing speed.

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	

Comments on the ACD:

committee-discussion

Interferon beta-1b and best supportive care are the relevant comparators

However, the NHS commissioning expert clarified that the NHS does not commission these drugs for secondary progressive multiple sclerosis and therefore they should not be considered relevant comparators.

I have trouble with this argument as the patients start the DMT during the relapsing phase of MS. Then it is very difficult to know whether/ when they have entered SPMS with certainty. It is therefore inevitable that some people remain on those DMTs during SPMS even though they may not be commissioned to start in people with SPMS.

The company suggests that its modelling does not capture additional benefits, but has not presented this evidence to the committee

cognitive processing have not been captured in the modelling

I agree that this effect has been rather downplayed in the appraisal and is of high relevance to people with MS. It is a common and disabling symptom that has a considerable impact on independence. It may be worthy of greater consideration.

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	

Comments on the ACD:

Has all of the relevant evidence been taken into account?

Mention is made of Beta-Interferon as an alternative drug but no account appears to have been taken of the significant increase in convenience of Siponimod (in tablet form) over Beta-Interferon (requiring a solution to be mixed and self-injected, both activities becoming increasingly difficult for a patient losing mobility/ feeling in hands).

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

The consultation document is silent on the loss of tax revenue to the exchequer in the event of the carer having to give up or reduce employment hours in addition to that of the patient's. It is also silent on the likely increase in monetary state benefits payable such as Personal Independence Payments made to MS patients experiencing increasing mobility loss and daily living issues (disability). The cost of Beta-Interferon as a comparable has also not been mentioned although one may infer that it is cheaper.

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

Don't feel qualified to answer this as a lay person - I have responded as an interested person given that I am suffering from SPMS.

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?

On the grounds of disability it should be noted that mixing a solution and self-injecting such as is required for Beta-Interferon is much more difficult for a disabled patient than an able-bodied patient. This should be compared with Siponimod which can be taken in tablet form (I currently have no problem swallowing).

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	

Comments on the ACD:

Has all of the relevant evidence been taken into account?

I would suggest that it is wrong to consider that most patients with secondary progressive are not on a disease modifying treatment. There has been little study on the effects of stopping disease modifying treatments in secondary progressive multiple sclerosis but most MS clinicians will have experienced deleterious outcomes in many patients who have come off disease modifying treatment and will thus be reluctant to recommend stopping treatment until patients are advanced in disability or to even classify secondary progressive disease until a much later time point in the condition. If siponimod were made available as a treatment then this may allow clinicians to treat patients with early secondary progressive disease with a therapy that is proven to slow progression, as opposed to continuing a therapy that may just benefit relapses and may even be more expensive than siponimod such as natalizumab or fingolimod.

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

I would suggest that the economic benefits of slowing disease progression should be considered in a broader sense, such as the benefits effects on employment status and need for social care.

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

Siponimod is a treatment that the rest of the developed world are using to treat active secondary progressive multiple sclerosis and thus I would suggest it is wrong for Siponomod not to be used in the UK.

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	

Comments on the ACD:

Has all of the relevant evidence been taken into account?

No. The key issue is that there is no effective treatment for SPMS - Betaferon is 20 years old, one of the least effective DMTs and is used by only a tiny number of patients. Therefore the comparison is not valid.

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

No. You have not factored in the huge, ongoing costs of social care and the NHS which could be alleviated through effective treatment.

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

No. You are denying SPMS patients the opportunity for effective treatment and leaving neurologists with no treatment options. According to your own data, there are 9000 SPMS patients in England who are being left forgotten.

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?

SPMS primarily affects older people. You are therefore discriminating against a group of people on the grounds of age.

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	

Comments on the ACD:

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

No I don't believe so. See comment below.

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

No. See below. I think they restrict treatment choice for people with MS and the clinicians caring for them.

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

Recommendations 1

Much is made in the recommendation that siponimod should be compared with best supportive care or interferon beta 1B. As a clinician looking after patients with MS I see an unmet need particularly in the group of patients who have been on a DMT for RRMS but may be transitioning to SPMS. It acknowledged in the

appraisal that many of these patients are not diagnosed with SPMS to enable them continue with DMT. This is partly because it is very difficult to determine when the risk of relapse has passed and it is therefore safe to stop a DMT without the risk of relapse. RRMS and SPMS are a continuum of the same disease. If a person is on a DMT for RRMS we cannot be sure if they are not relapsing because of the drug or because of the natural history of the disease is to have less obviously inflammatory activity later in the disease. Patients who have disease progression on DMT may still have relapses if DMT is stopped and it is these patients especially who would potentially benefit more from Siponimod than their current DMT. The results from the EXPAND study suggest benefits to patients with progressive disease in terms of reducing brain atrophy, a potental effect on remyelination and particularly on preserving cognition.
Having siponimod as an option for active SPMS patients not on treatment already is also really important. Many patients previously labelled as SPMS who have significant relapses and/or MRI activity may have their disease reclassified as RMS to be eligible for current DMTs. This is another reason why comparing against supportive care or IFN beta 1B is potentially misleading.

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	

Comments on the ACD:

Has all of the relevant evidence been taken into account?

No.

The conclusion reached by NICE ignores the evidence:
- Siponimod has proven to slow down disease progression significantly.
- Siponimod has additional benefits in reducing cognitive impairment.
- Ignores the preventative benefits of taking Siponimod early on to avoid irreversible disability setting in.

Assumes interferon beta is an alternative/existing treatment for SPMS patients, although most are not prescribed interferon beta due to how aggressive/intrusion the infusions are, and difficulties in administering the treatment.

The study does not consider the possible (positive) interaction with complementary treatments such as Fampyra, which can enhance the beneficial effects of Siponimod on disability management/reduction.

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

o.

1) Clinical effectiveness
The conclusion ignores the benefits from SPMS:
- Evident /significant slowdown in disease progression.

- Preventative benefits from slowing down disease progression, reversing cognitive impairments, thus maintaining independence of SPMS sufferers for longer.
- Siponimod is the only available treatment for SPMS. Interferon Beta, used in the study as a comparative, is not widely prescribed as infusions are not well tolerated and very intrusive to administer.

2) Cost effectiveness:
The conclusion ignores the costs of managing someone with SPMS where the disease is active and irreversible disability is progressing has not been taken into account:
- Cost saving from preventative benefits of using Siponimod. NICE's approach is to wait until the MS patient is so badly advanced that they lose their independence, and become entirely dependent on the state and NHS for housing, for carers, for benefits and for healthcare; these costs are far greater on the NHS than the cost of prescribing Siponimod to slow down disease progression/disability and delay the period where SPMS sufferers are fully dependent on the state, the NHS and others.
- Costs from the impact on relatives / carers of SPMS patients. Someone suffering from SPMS has a strong negative knock-on impact on their relatives, who have to provide care for their loved one, and as a result have to stop working to look after them.
- The extra burden on the NHS from:
    - Dealing with mental health issues from relatives of SPMS patients, who have to manage the decline of their relative suffering from SPMS
    - Managing additional deterioration of SPMS sufferers resulting from the issues experienced in finding regular, reliable, competent carers and accommodation, which results in a lot of SPMS sufferers becoming extremely isolated, and declining physically and cognitively faster than otherwise as they are not able to get the care they need.
- The cost comparison of Siponimod vs interferon beta, ignores the costs from the additional medical support needed to administer the infusions/injections, and severe side effects from interferon beta.

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

The cost effectiveness argument does not take into account the additional costs to the NHS and to the state of letting SPMS patients deteriorate without treatment, and ignores the preventative benefits from early administration to SPMS patients in maintaining their independence. The cost comparison to interferon beta is not relevant as interferon beta is not widely prescribed due to how intrusive it is.

The health benefits and positive effect on SPMS patients and their relatives/carers are also ignored in the conclusion reached by NICE.

The trial did not consider the possible (positive) interaction with complementary treatments such as Fampyra, which can enhance the beneficial effects of Siponimod on disability management/reduction.

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?

Yes.

Discriminates SPMS patients who have been given no treatment vs those that were given access to Siponimod on the NHS before this guidance was issued (and those in US and Europe who were given access to treatment due to Siponimod having been licensed there!).

This should be overruled and Siponimod should be made accessible to all SPMS patients on a discretionary basis, regardless of this guidance.

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	

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

Most of the drugs available for RRMS have no direct comparison for effectiveness (or are compared against Betaferon, which is much less effective than most drugs now available), but have been approved. There are so few treatment options for secondary progressive MS, I can't understand why Mayzent has been dismissed.

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	

Has all of the relevant evidence been taken into account?

No, patients with secondary progressive ms are reluctant to take beta interferon, and only 75 take it in England. There must be a reason for this

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

Cost effectiveness... my father paid voluntary nhs contributions whilst he was working in Europe with a hope he would be able to get treatment to slow down the disease progression but unfortunately died from the disease at the age of 58. I have been recently diagnosed, currently receiving tysabri, have paid national insurance since the age of 16 (I am now 37), will I have treatment denied because it is more expensive than and alternative that is ineffective

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

Not really, as only 75 people take the current treatment for SPMS. medical professionals are unsure of the efficacy of beta interferons and considering siponimod from initial trials has shown to reduce and slow disease progression It needs to be considered

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?

Disability and age need to be considered. I don't think it is appropriate to discount treatment because it is too expensive and that the patient is getting old

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	
Recommendations The only alternative is interferon Beta 1b which some patients, such as myself, have previously used unsuccessfully. Interferon Beta 1b is a treatment I started in 2009 as a newly diagnosed person with multiple sclerosis. It caused a side effect of severe clinical depression and had no positive effect on my multiple sclerosis relapse rates.	

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	
I think your refusal of this drug is very short sighted. There is nothing else on the market for spms that slows progression. You mention interfon but hardly anyone with spms gets this prescribed. It's an old drug, with no evidence of slowing down progression in spms. Medication and therapy cost thousands of pounds to treat the progressing symptoms of spms. The NHS could SAVE thousand by delaying this progression. This was the only hope for many with spms and you have taken that away without any thought of the ongoing costs of progression. If people were given this as the norm as they transition into spms you would save on all the medications and therapies they need as they progress.	

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	

Comments on the ACD:

Has all of the relevant evidence been taken into account?

No.

- Ignores the widely seen success of Siponimod for SPMS sufferers, which has been approved in the US and Europe.
- Ignores the preventative benefits of starting the treatment early in slowing down disease progression and irreversible onset of disability.

- Ignores the fact that there are no other treatments available for individuals with active SPMS; interferon beta-1bs are prescribed mostly for Relapsing Remitting MS, and in practice many patients are not prescribed interferon beta-1bs as they cannot tolerate the aggressive infusions of interferon beta-1b.

- Does not take into account potential positive benefits of combining Siponimod (which reduces disease progression and improves cognitive abilities) with Fampyra (which improves fluidity of movements).

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

No.

1- Clinical effectiveness

- Ignores the evidence of significant slow down of disease progression and proven improvement of cognitive abilities.

- Comparing Siponimod to interferon beta-1bs is irrelevant as very few SPMS sufferers are taking interferon beta-1bs, due to how invasive and aggressive the injections are on the body / poor tolerance.

- Ignores the fact that interferon beta-1b interacts negatively with the supplements taken to help manage SPMS symptoms (e.g. Vitamin D), as well as the side effects of interferon beta-1b infusions have aggressive side effects (e.g. skin reactions / infections from the injections, difficulty swallowing/breathing, extreme tiredness, muscle tightness, depression, hallucinations) which cancel out the benefits from the medicine.

- In addition, with COVID19, the side effects of interferon beta-1b (flu like symptoms) increase the risk that symptoms due to covid will be dismissed as a side effect of interferon beta-1b, putting SPMS patients at higher risk.

2- Cost effectiveness

- The cost comparison between Siponimod and interferon beta-1b ignores the costs associated with administering interferon beta-1b (infusion requiring a team of medically trained staff, hospital/clinic space, transport to be arranged

to/from hospital for SPMS patient) vs. Siponimod which is a non-invasive daily tablet that can be taken from home without medical assistance.

- Costs of the state and NHS having to look after SPMS sufferers as their disability increases has not been taken into account (medical care, further interventions to manage their symptoms, benefits as they can no longer work, accommodation as they need accessible/adaptable units to live in, carers, etc.).

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

No.

- The conclusions/recommendations do not take into account key evidence of the effectiveness of the drug to delay disease progression and the preventative effects of prescribing it early, and ignores the benefits of non-intrusive treatments for individuals with SPMS and the additional costs to the NHS and the state of leaving someone with SPMS to deteriorate.

- The drug is critically therapeutic to SPMS patients with evidence of active disease, and has a tangible positive impact on their life and prospects of keeping some form of independence.

- The conclusions also omit the fact that the Siponimod trial included a small proportion of UK based individuals, whose supportive care will vary greatly from the countries represented in the trial, therefore the results are not meaningful for the UK population.

- The conclusions do not consider the potential positive benefits of combining Siponimod (which reduces disease progression and improves cognitive abilities) with Fampyra (which improves fluidity of movements).

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?

Yes.

- Discrimination of those with SPMS who were not offered Siponimod on the NHS prior to this guidance being published. They have the same condition, however are not given the same treatment opportunities under NHS, which is discriminatory.

- This also does not take into account the individuality of SPMS and how Siponimod can be very effective on some patients. Those patients should be offered the chance to be put on the medicine, at the discretion of the medical team following each SPMS patient.

- e.g. in my case (I suffer from SPMS), I am a very good respondent to Fampyra, and have a medical profile that would make me a very good respondent to Siponimod as well. I was never offered interferon beta-1bs as the infusions were deemed too intrusive / aggressive on my body. Due to an administrative error with the National Hospital for Neurology and Neurosurgery, which is taking care of me in [redacted], I was never signed up to the Siponimod drug trial, despite having been assured multiple times that the necessary arrangements were being made, and so was taken away the chance at delaying any disease progression, despite the fact that Siponimod is susceptible to have very good results on someone like me.

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	
Has all of the relevant evidence been taken into account? No. Quality of life has not. This is one of very few possible DMTs for people with 2PMS. The option of an easy and quick to take tablet Vs a daily injection with known injection site issues should be taken into account. Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence? No. Quality of life has not. This is one of very few possible DMTs for people with 2PMS. The option of an easy and quick to take tablet Vs a daily injection with known injection site issues should be taken into account. Are the recommendations sound and a suitable basis for guidance to the NHS? No. Quality of life has not. This is one of very few possible DMTs for people with 2PMS. The option of an easy and quick to take tablet Vs a daily injection with known injection site issues should be taken into account.	

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	
information-about-siponimod Price e list price for siponimod is £1,648.23 per pack of 28 tablets, each containing 2 milligrams (excluding VAT; BNF online, May 2020). The company has a commercial arrangement, which would hav testing system works following clinician feedback that comments could not be submitted - please delete from collated comments	

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	
This is just to give insight in to practice in a Large Scottish unit, and difficulties around managing secondary progressive MS. We have not used beta interferon 1b for a long time due to high incidence of NABs and modest treatment effect. We agree that MS phenotypes are a spectrum of same condition with variable combination of inflammatory and degenerative pathology. Unfortunately the Lublin modification of MS classification has not been widely adapted and treatment trials segregate patients in to relapsing and progressive and largely progressive patients being excluded from trials, until recently. It is clear that inflammatory activity occurs in progressive patients and is amenable to immunomodulatory treatment. Currently we offer patients with secondary progressive MS, one of the licensed treatments (for RRMS) or rituximab, if there is evidence of inflammatory activity based on MRI scans and/or CSF neurofilament light chain levels. This is done through peer review and Individual Patient Treatment Request scheme. Also it may be unhelpful; to re-categorise these patients in to RRMS, as it is important to recognise that these are perhaps older individuals with progressive disability, and with different treatment related risk, and may muddy natural history studies. Thus, a licensed treatment for active secondary progressive MS will be welcome development, presuming it is cost effective.	

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	
Recommendations 1 MS Academy completed a survey amongst its members. 50 subjects responded of whom 42 did not agree with NICE's decision not to recommend siponimod for treating secondary progressive multiple sclerosis with evidence of active disease (that is, relapses or imaging features of inflammatory activity) in adults. Interferon beta-1b is the only disease-modifying treatment available for people with active secondary progressive multiple sclerosis. However, few people take it. Most people do not have any disease-modifying treatment. MS Academy disagrees with this statement as it doesn't represent current MS practice amongst UK neurologists who sub-specialise in MS. In our survey three-quarters (73%) of MS experts actively avoid diagnosing SPMS in patients on	

existing DMTs so as not to stop their DMT. Only 42% of respondents actively screen for SPMS when seeing patients on DMTs. The vast majority of neurologists (86%) are reluctant to stop DMTs in patients with SPMS on DMT because of concerns about rebound clinical and MRI disease activity and accelerated progression of the disease. Ninety percent of respondents thought it was inappropriate to stop DMTs in patients who have transitioned to becoming secondary progressive to see if they became active, i.e. potentially eligible for siponimod.

Our survey implies that a large number of patients with SPMS are on existing DMTs, who may become eligible for siponimod on stopping their current DMT. However, most neurologists would be reluctant to stop the current DMT because of the potential for rebound disease activity. The MS Academy urges both Novartis and NICE to take this catch-22 situation into account when modelling the cost-effectiveness of siponimod for its licensed indication. The practice highlighted by our survey suggests that patients with early SPMS on existing DMTs, with evidence of active MS, should be eligible for switching to siponimod. These patients are not only represented by patients on interferon-beta-1b.

MS Academy survey showed that 78% of neurologists don't switch patients on existing DMTs onto interferon-beta-1b. If NICE uses a network analysis it may be worth extending the analysis to other DMTs.

MS Academy urges NICE and Novartis to find a way of making siponimod cost-effectiveness for the treatment of active SPMS. Patients with SPMS feel disenfranchised and having a licensed DMT as a platform therapy for SPMS will allow the MS community to develop add-on therapies to target so called non-inflammatory mechanisms that are thought to contribute to progressive MS

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	

Comments on the ACD:

Has all of the relevant evidence been taken into account?

Yes, in the traditional sense as per NICE- primary and secondary outcome measures have been taken into account.

Exploratory outcome measure like cognition has not been taken into account which is an important aspect for patients' quality of life, implications for employment i.e continued to work and staying to be employed and dependence on carers and social care. Another aspect is to be aware of the implications availability of Siponimod will bring is better connect with the correct and earlier diagnosis of SPMS which aligns with the biological evidence

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

A clinical summary is reasonable.

It is fair to view the cost-effectiveness in the way the committee has when comparing to beta-interferon, though it will be difficult to do is a head-to-head comparison with beteferon as there are less than 100 patients in the whole country on betaferon.

What NICE cost-effectiveness calculations do not take into consideration is indirect effect/benefit these treatments bring in order to improve the care of secondary progressive MS patients. What the availability of Siponimod can bring to the table is apart from the obvious avaiablity of disease modification treatment for the patients who are on none similar, but also an opportunity of service development in various MS clinics in the country if costed sensibly, a phenomenon seen with the availability of other MS treatments seen in the past.

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

I am sure I and my patients would have liked the opportunity to have access to the treatment - clinically it works- works well on cognitive functions, works well on brain atrophy, and prevents brain volume shrinkage- within its limitations. Is there a possibility of price negotiations with the company to have a better cost-effectiveness equation? Perhaps the provision of evidence of positive effects on confirmed disability progression for a longer duration than the company may have or can collect might help the cause too.

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?

Nope

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	

Comments on the ACD:

Has all of the relevant evidence been taken into account?

The effect on serum neurofilament light chain levels should be considered.

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

I disagree with the clinical sections that I've already commented on.

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

There is an issue here as
the scientific principals on which the guidance are based on are not current with the understanding of the pathophysiology of MS. Siponimod, if licensed will be prescribed by MS specialists who understand this well and therefore do not make sense.

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?

In my opinion the decision for licensing should be based on scientific evidence, and Siponimod shows great promise in this context. By blocking at the outset, you are also in danger of blocking further drug development in this area of progressive disease. You are therefore, greatly disadvantaging this group of individuals.

committee-discussion

The diagnosis of secondary progressive MS is clinical classification of MS as relapsing-remitting (active) and secondary progressive (no longer active) has been made redundant by the discovery that there is ongoing inflammation in those previously thought to be progressive, and we may be dealing with one disease continuum rather than two distinct disease entities. Therefore, the efficacy of Siponimod in MS as a whole should be interpreted in this context. Siponimod, has anti-inflammatory properties and has been demonstrated to be efficacious in a group of individuals with ongoing inflammation that would otherwise not been eligible based on clinical classifications. The data on serum neurofilament light chain levels (a biomarker of subclinical inflammatory activity) which is reduced after Siponimod treatment backs up this hypothesis; https://multiplesclerosisnewstoday.com/2018/04/17/siponimod-reduces-levels-of-disease-activity-biomarker-in-spms-patients/. This strategy clearly makes a difference in the sub group of active progressive MS patients, delaying time to wheelchair use; https://multiplesclerosisnewstoday.com/news-posts/2019/09/06/ectrims2019-talk-158-siponimod-delays-the-time-to-wheelchair-in-patients-with-spms-results-from-the-expand-study/.

Siponimod could change the timing of diagnosis of secondary progressive multiple sclerosis and involve an MRI scan

This is true, but in itself is a circular argument. If a treatment was available for progressive MS, then the way to monitor it would be via MRI. This is a point of neurology practice and judging treatment efficacy and shouldn't be used as arbitrator for whether or not a treatment should be made available. In my opinion, we should not bias the availability of treatment for active secondary progressive MS based on resource issues. The overall burden on resources in the long-term would in fact be small as only those demonstrating active disease initially will have repeat scans going forward. This was not a factor in the decision process for primary progressive MS with Ocrelizumab and shouldn't be for secondary progressive MS. Moreover, we shouldn't adversely disadvantage this disease category alone in the UK, particularly when it has been licensed in other parts of the world.

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	

Comments on the ACD:

Has all of the relevant evidence been taken into account?

No
I suspect that the resource requirement for MRI scan has been miscalculated. All our patients in the SELKAMS area on high efficacy DMT's have yearly MRI scans. For other patients on DMT, the minimum requirement is biannual MRI.

The second point is about brain atrophy and cognition which is a significant factor in job retention for many patients. It seems that the 83% reported reduction in the cortical loss has not featured in the calculation.

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

Cannot answer without a background in statistics.

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

No
Many patients are being treated as 'transitional MS' with high-cost DMT as clinicians are cautious about removing the RRMS label due to lack of appropriate alternatives. Making Siponimod available to NHS will fill this gap.

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

Title: *Multiple sclerosis (secondary progressive) - Siponimod [ID1304]: ERG's response to the company's ACD response*

Produced by	Warwick Evidence
Authors	Peter Auguste, Research Fellow, Warwick Evidence Alexander Tsertsvadze, Senior Researcher, Warwick Evidence Mubarak Patel, Research Assistant, Warwick Evidence Chris Stinton, Senior Research Fellow, Warwick Evidence Felix Achana, Senior Research Fellow, Warwick Evidence Jacoby Patterson, Senior Researcher, Warwick Evidence Rachel Court, Information Specialist, Warwick Evidence Anna Brown, Information Specialist, Warwick Evidence Olga Ciccarelli, Professor of Neurology, University College of London Carl Counsell, Clinical reader, University of Aberdeen Xavier Armoiry, Honorary Clinical Research Fellow, Warwick Evidence Aileen Clarke, Professor of Public Health, Warwick Evidence Amy Grove, Assistant Professor, Warwick Evidence
Correspondence to	Dr Amy Grove A.L.Grove@warwick.ac.uk
Date completed	07/08/2020

Source of funding: This report was commissioned by the NIHR Evidence Synthesis Programme as project number 12/97/79.

Declared competing interests of the authors

Prof. Carl Counsell received funding through Biogen-Idec, who provided some funding for a departmental MS nurse.

Prof. Olga Ciccarelli received consultancy fees from Novartis, Biogen-Idec and General-Electric, Genzyme, All payments were made to her employer, UCL Institute of Neurology. She also received reimbursement for attending a symposium from Novartis and ECTRIMS, and funds for research from the UK MS Society, EPSRC, UCLH and BRC.

Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

Contributions of authors

Introduction

In Section 1 of this document we provide ERG responses to comments 1-8 included in the company response to ACD, the revised economic model and supporting Appendix. In Section 2 we provide a summary and critique of the new evidence and/or analyses submitted by the company in response to ACD.

1. Section 1

Comment number 1: Introductory text

No comment required.

Comment number 2: Due to a hesitancy by clinicians to formally diagnose SPMS, many patients who would be eligible for siponimod are still diagnosed and treated as having relapsing-remitting multiple sclerosis (RRMS)

The ERG support the view that there is "*uncertainty and hesitancy around diagnosing patients as having SPMS*".

We refer to Section 3.3 (Comparators) of the ERG report where we stated "The ERG do not consider interferon β-1b to be the only/most relevant comparator, as other DMTs could potentially be used to treat patients in the NHS (as descried in the NICE final scope "disease-modifying therapies used outside their marketing authorisations")".

In their response to ACD the company state that "*many patients who would be eligible for treatment with siponimod are likely to still be formally diagnosed as having RRMS and therefore still receive their RRMS DMT*." We agree with this point but question the evidence provided by the company to support it. The company provided evidence to suggest that "[redacted] *of sampled active SPMS patients were currently receiving treatment, compared with* [redacted] *of sampled patients with non-active SPMS*.[3]" As the assumption that [redacted] of patients with active SPMS are receiving a DMT is used to inform a scenario analysis (a weighted ICER for the analyses versus BSC and Extavia®) we checked this assumption with our clinical advisors and received mixed responses, that [redacted] was 'about right' to 'too high'. However, both confirmed that in the NHS, a proportion of RRMS patients would continue to receive DMTs ('half on low efficacy drugs and half on medium/high efficacy' and 'not be on an interferon but on a newer DMT') once diagnosed with SPMS.
For information, their exact responses were as follows:

1) '[redacted] is too high also if you considered that only about 10-15% of all RRMS in the UK are currently treated (The UK MS Society highlighted the small percentage in the past). Not more than 30% of SPMS are currently treated and half of them are on low efficacy drugs and half on medium/high efficacy, exactly as reported by the international MSBase analysis' A citation was provided (see 1a).

    a. Lizak, N., Malpas, C.B., Sharmin, S., Havrdova, E.K., Horakova, D., Izquierdo, G., Eichau, S., Lugaresi, A., Duquette, P., Girard, M. and Prat, A., Association of Sustained Immunotherapy With Disability Outcomes in Patients With Active Secondary Progressive Multiple Sclerosis. *JAMA neurology*.

2) 'I suspect the figures will vary greatly by UK centre but as the use of DMTs in relapse remitting MS grows so too will the use in SPMS as it can be difficult to stop Rx once people go into SPMS even in those with no active relapses. But these figures "feel" about right but as I say may be

higher in centres using a lot of DMTs. Given that people will usually stay on the DMT they are already on when they go into SPMS, many now will not be on an interferon but on a newer DMT so that assumption is certainly conservative, cost wise'.

Comment number 3: Siponimod is an innovative treatment offering cognitive benefits for patients in a phase of MS where there are currently limited to no treatment options

Section B.2.6.6 of the company submission reports the SDMT results of EXPAND. The ERG note that there was a reported improvement in SDMT in the siponimod group at Month 12 and Month 24 compared to placebo. At month 12, there was a [redacted], which increased to [redacted] for mean change in correct responses between siponimod and placebo. The ERG acknowledge the reported long-term SDMT data (up to 5-years) from the open-label extension phase of EXPAND, but note the uncertainty of this open label extension data as there was no comparator arm to assess the relative treatment effect.

The ERG have no further comment outside of those in the ACD regarding cognitive benefit, EQ-5D does not capture cognitive processing speed and therefore, cognitive processing speed is not accounted for in the economic model.

Comment number 4: The economic model already captures neurology appointments for patients with active SPMS

The ERG clinical advisor confirmed the gradual transition between RRMS and SPMS, the diagnostic criteria is imprecise and variable, and made using clinical and imaging features. The company submission did not provide a description of the MRI sequences used for characterising MS severity and progression.

The ERG confirm that the original economic model already included two neurology appointments associated with siponimod treatment each year, including both a higher cost of a first appointment as well as a follow-up appointment in Year 1. The revised model incorporates the cost of one additional MRI scan (i.e., third) for all patients receiving siponimod as a scenario.

Comment number 5: European Study Group (EU) study matching-adjusted indirect comparison (MAIC) results in a less robust and more uncertain comparison than the North American study MAIC

The ERG note that the company included the European study (EU) study in their MAIC results for 3-month confirmed disability progression (CDP) and ARR (Section B.2.9.4 of Document B, Table 41 CDP and Table 42 ARR).

The ERG support the view highlighted in ACD regarding the value of using data from the EU study in the MAIC analysis (European Study Group 1998). The company however, notes that the MAIC results using data from EU study are less robust and more uncertain than MAIC using data from North American (NA) study (Panitch et al. 2004). Evidence to support our view is provided below:

1) One of the concerns raised by the company relates to the evidence that even if the EU study has a larger proportion of relapsing patients than the NA study, the EU study population is considerably younger (mean age: 41.0 years) than the NA and EXPAND ITT study populations

(mean age: 46.8 and 48.0 years, respectively). The ERG note that the mean age of EU study population (41.0 years) is based on the total study sample, not the subgroup of supposedly Active SPMS (i.e., patients with relapse). Considering that the EU study included patients with ages ranging from 18 to 55 years, it is not implausible that the mean age of Active SPMS patients in EU study would be above 41 years. However, this cannot be verified as the mean age of the subgroup of patients with Active SPMS in the EU study is not reported.

2) In the company MAIC included in the company submission, matching for inclusion/exclusion criteria for age between EXPAND (age range: 18-60 years) and other studies was achieved for EU study (age range: 18-55 years), but not for NA study (age range: 18-65 years), because the criterion for age range was narrower in the EXPAND vs. NA study. The company matched the EXPAND and EU studies on the age range of 18-55 years, thereby supporting the validity of MAIC results by removing the effect of age (excluding patients >55 years old). The ERG, note that the results of the MAIC based on EU study may not be readily applicable to Active SPMS patients older than 55 years.

   Similarly, the definition of SPMS active disease as the inclusion criterion was sufficiently comparable (but not identical) between the EU and EXPAND studies in order to be matched in the MAIC analysis (Company Appendix, Table 32, page 99). Given the lack of similar definition in the NA study report, no such matching was possible between EXPAND and NA study (Company Appendix, Table 26, page 93).

3) The EU study publication provides evidence indicating that the EU study enrolled patients with Active SPMS: "*a recorded history of either two relapses or more or 1.0 point or more increase in EDSS in the previous 2 years*" (Patients and treatment section, page 1492) (European Study Group 1998), whereas the paper describing NA study inclusion criteria stated: "*a history of at least one relapse followed by progressive deterioration sustained for at least 6 months*" (Subjects and treatment section, page 1789) (Panitch et al. 2004) without specifying a time window for the occurrence of relapse prior to study entry.

   Furthermore, the EU study characterised patients included in their study as follows "*Patients were in the early stage of progression beginning about 10 years after initial diagnosis of MS and had active disease in the 2 years before entry into the study*" (Discussion section, page 1496) (European Study Group 1998). No such statement defining active disease can be found in the NA study publication. The mean number of relapses in 2 years prior to NA study was 0.8 (Table 2, page 1791), which indicates the NA study sample consisted of very few or no patients with active SPMS (Panitch et al. 2004).

The ERG's view that the NA study included predominantly non (or less)-active form of SPMS is corroborated by the company in their original 'Siponimod vs. IFNβ-1b (Betaferon®): North American Study' comparison conclusion (Document C Appendix, page 98): "*The North American Study did not include an active SPMS subgroup and the overall population was not considered to represent an active SPMS population closely enough for a MAIC or ITC in this population to be robust*."

Current therapies indicated for relapsing forms of MS (interferon beta-1a/1b, natalizumab) are not recommended for the treatment of non-relapsing SPMS (non-active form) due to their lack of efficacy in terms of delaying the progression of disability. The natural course of MS progression has been shown to exhibit decline in disease activity (relapses/MRI based lesions) coinciding with maintained gradual progression in disability over time. The NA study population were older, had a longer duration of MSPS (later stage of SPMS), and thus less active disease compared to patients in EU study. Therefore, the NA study results were consistent with those of other studies that included predominantly (>50%) patients with non-relapsing SPMS in failing to show the treatment benefit of current therapies in slowing down the

disease progression compared to placebo (Kapoor et al., 2018; SPECTRIMS MS Study Group 2001, Cohen et al. 2002).

Regarding the primary outcome of CDP measured in the EU (time to 3-month CDP) and NA studies (time to 6-month CDP), the company state that "*NICE has consistently favoured the use of 6-month CDP as a more appropriate measure of progression in previous MS technology appraisals*". The ERG acknowledge this important point but note that the CDP measured in the EU (time to 3-month CDP) and NA studies (time to 6-month CDP) is an endpoint which incorporates the measurement of the Expanded Disability Status Scale (EDSS) score. It is likely that the EDSS score and thus the time to CDP measurements were more reliable in the EU compared to NA study, due to the fact that in the EU study EDSS training was administered before the start and in yearly follow-up sessions of the study, whereas in NA study, the EDSS score measurement training was provided only at the start of the study.

Given all the points above, the ERG considers the baseline patient characteristics of the EXPAND study and EU study similar with results more relevant and generalisable to the NHS population with Active SPMS compared to NA study. The company conclude that "*using the EU study, 3-month CDP MAIC for comparing siponimod with interferon β-1b results in a less reliable and more uncertain comparison, with less applicability to UK clinical practice. As such, the EU study MAIC should not be considered an appropriate source of comparative efficacy for reimbursement decisions".* Overall, the ERG suggests that with all the uncertainties taken into account (e.g., low effective sample size, wide 95% confidence intervals around the estimate, across-trial differences in inclusion/exclusion criteria, baseline characteristics), the MAIC analysis using EU study data provides the most valid estimate of siponimod compared with interferon beta-1b.

Comment number 6: Treatment discontinuation rates should be utilised rather than study discontinuation rates

The ERG confirm that the revised model includes treatment discontinuation rates rather than study discontinuation rates.

Comment number 7: Utility values in the economic model should be based on Active SPMS utility values from EXPAND

The ERG confirm that the revised model has been updated to include Active SPMS utility values from EXPAND supplemented by Orme et al. (2007), rather than the ITT population.

Comment number 8: Efficacy in subgroups for people with Active SPMS with and without imaging features of inflammatory activity

The company state that there are [redacted] between the subgroups (Relapsing SPMS with MRI activity, Relapsing SPMS without MRI activity, Non-relapsing SPMS with MRI activity) in terms of effectiveness results (3- or 6-month CDP or ARR), nor in comparison to the overall Active SPMS population.

The ERG visually assessed the subgroup data provided in the company Appendix Tables 9-12 and conducted a visual inspection of the Kaplan-Meier (KM) curves provided in Figure 6-13. We reconstructed the survival IPD from the KM plots (Fig 6-13) and plotted scaled Schoenfeld residual vs. time graphs to asses any proportional hazards (PH) violations (Wei & Royston 2017). The ERG note that as this is reconstructed data this assessment provides an estimate at best, however we found no PH violations.

The baseline characteristics between-group mean (SD) or proportions provided in Table 9 visually appear to be [redacted] for each of the additional three subgroups.

Table 10 presents time to 3-month CDP for the three subgroups and Active SPMS. Although [redacted]. Therefore, there are [redacted] between siponimod and placebo for the subgroups. The 'Relapsing SPMS without MRI activity' subgroup was [redacted] (HR [redacted] 95% CI [redacted] P=[redacted]. Table 12 presents time to 6-month CDP comparison for the three subgroups. The ERG note that there are [redacted] between siponimod and placebo for the subgroups. Table 12 presents comparisons of 'Negative binomial regression of Annualised Relapse Rate (ARR) for confirmed relapses' across the three subgroups. The ERG confirm that there are [redacted] for ARR for the Relapsing SPMS with MRI activity (ARR Ratio [redacted] 95% CI [redacted] P=[redacted], and Non-relapsing SPMS with MRI activity subgroups (ARR Ratio [redacted] 95% CI [redacted] P=[redacted], but not for Relapsing SPMS without MRI activity subgroup (ARR Ratio [redacted] 95% CI ([redacted] P=[redacted]).

The ERG acknowledge the point that "*cutting the Active SPMS subgroup data into smaller subgroups, analyses are increasingly underpowered."*

2. Section 2

In this section the ERG provide a summary and critique of the new evidence and/or analyses submitted by the company. As part of the company's response to the ACD produced by NICE, the company submitted:

- An updated confidential patient access scheme (PAS) price
- An updated electronic economic model
- Updated utility values from the subgroup of people with active disease from EXPAND supplemented by Orme et al. (2007)
- An appendix that included:
    - A new base-case with the committee's preferences
    - A series of scenario analyses
        - An additional (3rd) neurology appointment in Year 1 for Siponimod
        - Active SPMS with source of efficacy from a network meta-analysis (NMA)
        - Treatment waning assumption was explored based on a tapered waning of 25% from Year 7, followed by 50% from Year 10, based on the available long-term efficacy data from EXPAND of up to six years
        - Active SPMS NMA and waning treatment from Year 7, followed by 50% from Year 10, based on the available long-term efficacy data from EXPAND of up to six years
        - Basket comparator: in which a weighted ICER is calculated for a mix of best supportive care and DMT comparators

2.1 [redacted]

[redacted]

2.2 Updated utility values from the subgroup of people with active disease

In Table 1 the company provided updated health state utility values derived from the subgroup of people with active disease, supplemented with values obtained from Orme et al., (2007).

Table 1. Summary of utility values for people with active disease

EDSS State	Active SPMS utilities	Source
0	0.825	Orme et al., 2007
1	0.754	
2	0.660	
3	[redacted]	EXPAND
4	[redacted]	
5	[redacted]	
6	[redacted]	
7	[redacted]	
8	−0.094	Orme et al., 2007
9	−0.240	
10	0	By definition
EDSS, expanded disability status score; SPMS, secondary progressive multiple sclerosis		

2.3 New base-case results

A revised probabilistic base-case analysis was submitted which included the committee's preferences:

- *Additional cost for magnetic resonance imaging (MRI) scan for people starting siponimod*
- *Active SPMS utilities as opposed to ITT utilities*
- *Treatment discontinuation as opposed to study discontinuation*
- *Matching-adjusted indirect comparison (MAIC) vs Extavia® using the North American study*
- *Treatment waning of 50% from Year 11 (in line with the assumptions used in NICE appraisal TA527)*

Incremental probabilistic results showed that treatment with interferon β-1b (Extavia®) [redacted] treatment with Siponimod. Siponimod is approximately [redacted] more costly than best supportive care and is expected to yield 0.84 more QALY, which equates to an ICER of approximately [redacted] per QALY (see Table 2).

Table 2. Company's revised probabilistic base-case results

DMT	Total costs	Incremental costs	Total QALYs	Incremental QALYs	ICER
BSC	[redacted]	-	2.75	-	-
Interferon β-1b	[redacted]	-	2.85	-	[redacted]
Siponimod	[redacted]	[redacted]	3.59	0.84	[redacted]
BSC, best supportive care; DMT, disease modifying therapy; ICER, incremental cost-effectiveness ratio: QALYs, quality adjusted life-years					

Table 3 presents the probability of each intervention being cost-effective at willingness-to-pay thresholds of £20,000 and £30,000, respectively. From the 1000 iterations, these results show that at a willingness-to-pay threshold of £30,000 Siponimod has a [redacted] probability of being cost-effective.

Table 3. Probability of each DMT being cost-effectiveness

Intervention	Probability of cost-effectiveness at a £20,000 per QALY threshold	Probability of cost-effectiveness at a £30,000 per QALY threshold
Siponimod	[redacted]	[redacted]
Extavia®	[redacted]	[redacted]
BSC	[redacted]	[redacted]
BSC, best supportive care; QALY, quality adjusted life-years		

In summary, the ERG understands that the committee's preferred assumptions have been applied appropriately in the company's base-case analysis along with an updated PAS agreement, thus the results are unlikely to contain an unbiased assessment of the cost-effectiveness.

2.4 Scenario analyses results

The company undertook a series of scenario analyses, which were outlined in section company appendix sections A.3.2-A.3.6:

A.3.2. Scenario: additional, third neurologist appointment in Year 1 for siponimod
A.3.3. Scenario: active SPMS NMA
A.3.4. Scenario: tapered waning from year 7
A.3.5. Scenario: active SPMS NMA and tapered waning from year 7
A.3.6. Scenario: basket comparator

Across all scenario analyses conducted, using the source of efficacy from the Active SPMS network meta-analysis (NMA) and waning of the treatment effect from Year 7 had the greatest impact to the ICER, which increased from approximately [redacted] to [redacted] for the comparison between siponimod and best supportive care.

References

Cohen JA, Cutter GR, Fischer JS, Goodman AD, Heidenreich FR, Kooijmans MF, et al. Benefit of interferon beta-1a on MSFC progression in secondary progressive MS. Neurology 2002;59(5):679-87.

European Study Group. Placebo-controlled multicentre randomised trial of interferon beta-1b in treatment of secondary progressive multiple sclerosis. European Study Group on interferon beta-1b in secondary progressive MS. Lancet 1998;352(9139):1491-7.

Kapoor R, Ho PR, Campbell N, Chang I, Deykin A, Forrestal F, et al. Effect of natalizumab on disease progression in secondary progressive multiple sclerosis (ASCEND): a phase 3, randomised, double-blind, placebo-controlled trial with an open-label extension. Lancet Neurol 2018;17(5):405-15. http://dx.doi.org/10.1016/s1474-4422(18)30069-3.

Orme M, Kerrigan J, Tyas D, Russell N, Nixon R. The effect of disease, functional status, and relapses on the utility of people with multiple sclerosis in the UK. *Value Health* 2007;**10**(1):54-60. http://dx.doi.org/10.1111/j.1524-4733.2006.00144.x

Panitch H, Miller A, Paty D, Weinshenker B. Interferon beta-1b in secondary progressive MS: results from a 3-year controlled study. Neurology 2004;63(10):1788-95.

SPECTRIMS MS Study Group. Randomized controlled trial of interferon- beta-1a in secondary progressive MS: Clinical results. Neurology 2001;56(11):1496-504.

Wei Y, Royston P. Reconstructing time-to-event data from published Kaplan-Meier curves. *Stata J*. 2017;17(4):786-802.