National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Siponimod for treating secondary progressive multiple sclerosis ID1304

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

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Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Appropriateness	Novartis	We consider it appropriate to refer this topic to NICE for appraisal.	Comment noted. No action required.
	MS Society	Yes. Siponimod has shown promising results in clinical trials, with siponimod significantly reducing the risk of a patient's disabilities worsening over a three-month period by over a fifth versus placebo. Only 26% people on siponimod experienced a worsening of disability while on EXPAND trial compared to 32% who took a placebo. As there are currently no licensed treatments for secondary progressive MS that slow progression, siponimod represents a potential ground breaking step in MS treatment.	Comment noted. The innovative nature of siponimod will be considered in any appraisal of the technology.
	MS Trust	Yes, we understand that the EMA CHMP is currently evaluating a marketing authorisation application for siponimod for secondary progressive MS. [redacted]	Comment noted. No action required.
Wording	Novartis	The licence wording is currently anticipated to be: [redacted]	Comment noted. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
		[redacted] Therefore, we consider the wording of the remit to be appropriate.	
	MS Trust	Yes, the draft remit reflects the issues that NICE should consider.	Comment noted. No action required.
Timing Issues	Association of British Neurologists	Routine	Comment noted. No action required.
	Novartis	Very limited treatment options are available to people with SPMS. Siponimod offers a treatment option in this area of high unmet need. We therefore believe that timely NICE guidance for siponimod would be valuable to the NHS.	Comment noted. The aim of the STA process is to provide guidance close to the MA being granted. No action required.
	MS Society	As siponimod is yet to be granted a marketing authorisation, the NICE STA must be aligned with the EMA's licensing schedule	Comment noted. See response to comment on Timing Issues by Novartis.
	MS Trust	Currently there are no licensed treatments that slow down or stop disease progression in secondary progressive MS. If a marketing authorisation is granted, there is likely to be a high demand for siponimod. It is vital that NICE appraisal is completed as close as possible to licensing to ensure clarity about eligibility and availability within NHS England. However the wording of the licensed indication may reference specific subgroups which would have a significant impact on the appraisal.	Comment noted. See response to comment on Timing Issues by Novartis.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Association of British Neurologists	It is accurate. It should be emphasised that it is unusual for pts with established SPMS to relapse and thus it would be rare for them to be started on interferon 1-b or steroid therapy.	Comment noted. The wording of the background information has been amended to indicate relative rarity of relapse in SPMS.
	MS Society	The background does not adequately capture the symptoms of secondary progressive MS and the impact such a diagnosis can have on individuals. Being told that you now have secondary progressive is often devastating news for a patient. In addition, as people become ineligible for current DMTs, people can lose touch with services, often due to the mistaken belief that nothing can be done. These are sensitive and challenging conversations for professionals to have with patients, and care management of SPMS can be complex due to the symptoms.	Comment noted. The symptoms listed in the background information cover RRMS symptoms and mention the increasing and more persistent disability associated with SPMS. The background section of the scope aims to provide a brief summary of the disease and how it is managed, and is not designed to be exhaustive. The nature of the condition will be considered in any appraisal of siponimod. No action required.
	MS Trust	Background does not adequately reflect the impact of secondary progressive MS (SPMS). A small number of people will be diagnosed with secondary progressive MS from the outset.	Comment noted. The wording of the background information has been amended to include this route of diagnosis. Comment noted. The symptoms listed in the background information cover

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		Many people find the transition from relapsing remitting to secondary progressive MS very challenging; this can feel like being diagnosed all over again. Symptoms include mobility problems, weakness, spasticity and spasms, bladder and bowel problems, sexual difficulties, and fatigue. Cognitive problems are more severe in secondary progressive MS compared to relapsing remitting MS, leading to lower quality of life. Other symptoms can include balance issues, visual problems, sensory problems (pain), tremor, speech and swallowing difficulties, depression and anxiety. Complications resulting from the interplay of symptoms can arise, for example, falls as a result of mobility and balance problems, pressure sores as a result of immobility etc. This requires expert knowledge and management. There are significant challenges to remaining in employment for people with SPMS and increasing carer burden as the condition progresses.	RRMS symptoms and mention the increasing and more persistent disability associated with SPMS. The background section of the scope aims to provide a brief summary of the disease and how it is managed, and is not designed to be exhaustive. The nature of the condition will be considered in any appraisal of siponimod. No action required. Comment noted. Carer burden will be considered in any appraisal of siponimod. No action required.
The technology/ intervention	Novartis	Novartis suggests replacing the following text in the Technology section: “The drug selectively binds to circulating lymphocytes which enables a reversible trapping of a proportion of lymphocytes in the lymph nodes, leading to a reduction in disease activity.” with: “The drug selectively binds to circulating lymphocytes which reversibly inhibits egress of lymphocytes from the lymph nodes, leading to a reduction in disease activity.”	Comment noted. The technology section has been updated.
	MS Trust	Yes, this is accurate. Brand name for siponimod is Mayzent. Siponimod crosses the blood brain barrier and binds to specific cells in the central nervous system (oligodendrocytes and astrocytes) which	Comment noted. The brand name has been updated.

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		are involved in repair of the myelin coating of nerve axons damaged by multiple sclerosis. This mechanism of action may contribute to the reduction in disability progression achieved by siponimod. Siponimod also improves cognition, through an improvement in information processing speed.	
Population	Association of British Neurologists	It is defined appropriately. A case could be made for separating those with SPMS and relapses and those without. However, the treatment has been shown to slow progression in both groups.	Comment noted. The technology will be appraised within its marketing authorisation. No action required.
	Novartis	The population is defined appropriately.	Comment noted. No action required.
	MS Trust	Yes, we agree that the population should be defined as people with secondary progressive MS. It is anticipated that this will include all people with secondary progressive MS, both relapsing and non-relapsing MS. The marketing authorisation may qualify the population further. In the EXPAND phase III study, patients were aged 18-60, had EDSS of 3.0 to 6.5, disability progression in the two years before the study and no evidence of relapse in the 3 months before randomisation. Sub-group analyses have been carried out (see below).	Comment noted. The technology will be appraised within its marketing authorisation. No action required.
Comparators	Association of British Neurologists	The main objective of this therapy is to prevent the accumulation of disability in patients with SPMS for which there is no licenced therapy. However most neurologists consider primary progressive MS to be the same as SPMS, the initial relapses being subclinical. If this were	Comment noted. Ocrelizumab does not have a marketing authorisation for secondary progressive MS. However, medicines used outside of their

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		accepted then ocrelizumab, which is currently undergoing an appraisal, would be an appropriate comparator.	marketing authorisations can be considered comparators, if they constitute standard care in the NHS. The comparator section has been updated to include established clinical management, including disease modifying therapies used outside their marketing authorisations.
	Novartis	Clinical experts have advised Novartis that the “diagnosis” of SPMS, i.e. the transition from relapsing remitting multiple sclerosis (RRMS) to SPMS, is very difficult to ascertain due to the unpredictability of the disease and fluctuation in symptom burden, and that this diagnosis has to be determined retrospectively. Given the uncertainty in timing of definitive diagnosis of SPMS and the limited treatment options available once a patient is diagnosed with SPMS, patients are typically kept on their existing disease modifying therapy (DMT) to allow them to benefit from treatment. Therefore, best supportive care is not a relevant comparator in clinical practice as patients eligible for siponimod are currently on DMT, either licensed for SPMS (such as interferon beta-1b) or for RRMS used off-label in SPMS. The standard of care for people with SPMS, and relevant comparator to siponimod, should therefore be: Established clinical management including disease-modifying therapies licensed for SPMS, such as IFN-beta-1b, and those used outside their marketing authorisation.	Comment noted. The comparator section has been updated to include established clinical management. Best supportive care has been removed.

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	MS Society	Interferon beta 1b should not be included as a comparators, as it does not address disability progression which siponimod does. Best supportive care needs to be clearly defined. However it also does not address progression, therefore not an adequate comparator.	Comment noted. The aim of the comparator section is to describe current clinical management for the entire population to be appraised, including people with active disease, evidenced by relapses. The comparator section has been updated to include established clinical management. Best supportive care has been removed.
	MS Trust	We do not believe that interferon beta 1b should be considered as a comparator; it reduces the number and severity of relapses and is licensed for patients with secondary progressive multiple sclerosis with relapses (active disease). In contrast, siponimod reduces confirmed disability progression independent of an effect on relapses (non-active disease) . Furthermore, the prescribing of interferon beta 1b (Extavia) is very low, especially in people with secondary progressive MS with relapses; 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. In practice, because there are no treatments for secondary progressive MS, clinicians delay diagnosis and continue to prescribe all of the disease modifying drugs beyond the transition from relapsing remitting to secondary progressive MS. For an accurate picture of the	Comment noted. The aim of the comparator section is to describe current clinical management for the entire population to be appraised, including people with active disease, evidenced by relapses. The appropriateness of all potential comparators will be considered in any appraisal of siponimod. Comment noted. The comparator section has been updated to include established clinical management, including disease modifying therapies

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		current cost to the NHS of treating secondary progressive MS, this appraisal must recognise that all of the disease modifying drugs continue to be used at least up until an established EDSS 7, even though this use is not strictly covered by licensing. As a minimum, a blended comparator of disease modifying drugs based on UK market share should be used. Best supportive care covers a huge range of interventions and should be more specifically defined. The NICE clinical guideline for MS (CG186) and the associated Quality Standard is a basis for this definition but should not be taken as representing the views of MS health professionals as constituting a comprehensive description of care for secondary progressive MS. There is no current evidence-based professional consensus on what constitutes best supportive care for secondary progressive MS or the associated cost. Management of secondary progressive MS focuses on four key areas: symptom management; prevention of complications; maintaining function and promoting general health and wellbeing. Given the wide range of symptoms that individuals with secondary progressive MS may experience, it is important that there is access to a range of therapies delivered by skilled allied health professionals, competent in MS care. These health professionals are generally engaged according to patient need for episodes of treatment focussed on individual problems and goals. In reality, access to NHS and social care interventions to support people living with MS such as physiotherapy or neurorehabilitation is limited, sporadic or even non-existent. The quality of and access to care is highly dependent on where someone lives. Calculation of the cost of providing best supportive care cannot assume an ideal situation where these services are readily available.	used outside their marketing authorisations. Best supportive care has been removed.

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		A key issue for defining best supportive care will be recognising the importance of continuous access to an MS team with a named single point of contact. In practice, this is generally an MS specialist nurse or an MS specialist allied health professional who is part of the larger multidisciplinary team. We are aware that many people with secondary progressive MS have been effectively 'discharged' from services, either due to a perception that there is no 'treatment' available for secondary progressive MS (by which clinicians generally mean disease modifying treatment) or due to limitations in service capacity. The role of neurorehabilitation services, including rehabilitation physicians is important to management of secondary progressive MS. This includes specialist rehab interventions such as vocational rehabilitation, which can make a significant impact on ability to remain in employment. Neuropsychology services are also in very limited supply. Survey data collected by the MS Trust shows that MS neurologists and MS nurses identify many of these therapy services as patchy or insufficient in their area (Improving services for people with advanced MS, November 2016, MS Trust, https://support.mstrust.org.uk/file/MSFV-AMS-report.pdf	

Outcomes	Association of British Neurologists	Yes with the exception of MRI parameters	Comment noted. The outcomes section of the scope has been updated to include MRI parameters of lesion counts and brain volume change.
	MS Society	These outcomes are correct but could be expanded. To gain a fuller understanding of disease activity a full range of indicators should be	Comment noted. The outcomes section of the scope

		acknowledged, both clinical and subclinical. Understanding of disease activity in MS is evolving, with greater emphasis being placed on symptoms beyond relapse rates and disability progression such as the number of lesions on MRI scans and brain atrophy. Further indicators should also be included. In 2015, a panel of MS experts proposed the inclusion of measures of cognition, fatigue and depression in the definition of disease activity, as these patient-reported outcomes contribute substantially towards quality of life in people with MS (Brain Health Report)	has been updated to include MRI parameters of lesion counts and brain volume change. Symptoms of SPMS are included in the list outcomes. The list is not exhaustive, therefore information on those specific outcome measures can be submitted.
	MS Trust	Composite measures of MS progression, combining data from timed 25 ft walk, 9 hole peg test, EDSS and others are emerging as more sensitive measures of disability progression compared to EDSS alone. Relapse rate and severity may not be an appropriate outcome measure; recent research suggests that disease modifying drugs used after conversion to secondary progressive MS have no substantial effect on relapse-unrelated disability outcomes measured by EDSS up to 4 years . MRI measures should be considered – the EXPAND study included lesions count and brain volume changes. Cognitive outcome measures should also be included.	Comment noted. The outcomes section of the scope has been updated to include MRI parameters of lesion counts and brain volume change. Symptoms of SPMS are included in the list outcomes. The list is not exhaustive, therefore information on those specific outcome measures can be submitted.
Economic analysis	Association of British Neurologists	The cost should include an estimate for the loss of economic activity from the patient as well as the family members that act as carers	Comment noted. Although wider societal costs are not included in the NICE reference case, the committee can consider the impact of the disease on patients and their families as part of the appraisal. No action required.

	MS Society	The statement, "costs will be considered from an NHS and Personal Social Services perspective" does not adequately address the costs to patients and carers or to society and the economy in general. MS can have a devastating effect on a person's ability to remain in employment and on the levels of informal care they require. A report by the Work Foundation found that up to 80 per cent of people with MS stop working within 15 years of the onset of diagnosis and 44 per cent retire early because of the condition (Bevan, S., Zheltoukhova, K., McGee, R. and Blazey L. (2011) Ready to Work? Meeting the Employment and Career Aspirations of People with Multiple Sclerosis. London: Work Foundation). The current average employment rate of people with mild MS is 37% and for people with severe MS it is 4% (Bajorek, et al.(2016), The impact of long term conditions on employment and the wider UK economy). There is a significant gap in employment rates between people with MS (36%) and the overall population (75%) in the UK, which means that people with MS may lose a significant number of working years (Kobelt et al (2017) New insights into the burden and costs of multiple sclerosis in Europe, Multiple Sclerosis Journal; Office for National Statistics, UK labour market July 2017). It must be taken into account that MS is a chronic progressive condition that has a significant impact on the quality of life of individuals with the condition and also the lives of family members. MS Society research suggests 85% of people with MS receive support or assistance from friends and family members (MS Society, Social care and the MS community in England, 2017). The committee should therefore take into account the potential impact of this treatment on: - the ability of unpaid carers to remain in the workforce and therefore increased tax revenue (Kennedy, 2009: 27)	Comment noted. Although wider societal costs are not included in the NICE reference case, the committee can consider the impact of the disease on patients and their families as part of the appraisal. No action required. Comment noted. The health benefits and adverse effects that are important to patients and, where relevant, carers will be considered in any appraisal of siponimod. No action required.

		- independence and quality of life of unpaid carers. The Work Foundation found that the "professional careers of 57 per cent of relatives are adversely affected by MS of a family member" (Bevan, S., Zheltoukhova, K., McGee, R. and Blazey L. (2011) Ready to Work? Meeting the Employment and Career Aspirations of People with Multiple Sclerosis. London: Work Foundation).	
	MS Trust	We recognise it will be challenging to calculate benefits over the longer term against the backdrop of a progressively deteriorating condition. Economic analysis does not take into account the societal costs of secondary progressive MS. Progressive disability has a significant impact on the ability to work or undertake normal daily activities. This is likely to lead to time off work (and potentially loss of employment) both for the person with MS and informal carers, resulting in a loss of productivity. In addition, when patients with secondary progressive MS are discharged from neurological services, development of complications due to inadequate management of symptoms in primary care will lead to further cost to the NHS.	Comment noted. Although wider societal costs are not included in the NICE reference case, the committee can consider the impact of the disease on patients and their families as part of the appraisal. No action required. Comment noted. The scope notes that the time horizon of an economic analysis should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. No action required.
Equality and Diversity	Novartis	No equality issues have been identified.	Comment noted. No action required.
Innovation	Association of British Neurologists	Whilst siponimod is similar to fingolimod it is the first treatment that has been shown to reduce the accumulation of disability in patients with SPMS – a significant advance. It will diminish the loss of economic productivity of patients and their family members that act as carers. This data should also be made available to the committee	Comment noted. The extent to which the technology is innovative will be considered in any appraisal of siponimod. The company will have an opportunity to provide evidence on the innovative

			nature of its product in its submission.
	Novartis	Siponimod is the only DMT which has been proven to delay disability progression in a typical hard-to-treat SPMS population, in which other DMTs have failed to demonstrate disability progression in clinical trials. As commented in the Comparators section, clinical experts have advised Novartis that the transition from RRMS to SPMS is very difficult to determine, and given this difficulty and the limited treatment options available for SPMS in the NHS, clinicians may be hesitant to "diagnose" SPMS if patients can benefit from continued DMT treatment. Therefore, availability of siponimod could create a step-change in the "diagnosis" and management of SPMS in the NHS, as clinicians may feel more confident to "diagnose" SPMS earlier if there is an effective, licensed DMT option. Some of the health-related benefits of siponimod are not captured in the QALY, such as beneficial effect on cognition, as demonstrated in the EXPAND clinical trial. The Expanded Disability Status Scale (EDSS) is the gold standard in evaluating disability in people with multiple sclerosis (MS) and is therefore used in clinical trials and cost-effectiveness analyses of DMTs for MS. Impaired cognition is an important aspect of MS symptom burden and although treatment impact on cognition may to some extent be captured in EDSS disability progression outcomes captured in the QALY, the EDSS has been reported not to be sensitive to changes in cognition.1 The EDSS score is primarily influenced by walking ability, especially in people with SPMS, and impact on cognition is therefore not accounted for in QALY calculation based on EDSS-related outcomes. 1. Gudesblatt et al 2016. Multiple sclerosis, EDSS, and objective cognitive function: a walking scale with no apparent brains and limited thought. ECTRIMS Online Library. Abstract: P365.	Comment noted. See response to comment on Innovation by Association of British Neurologists.

	MS Society	Yes. Siponimod becoming available for people with secondary progress would represent a step-change as the first licensed treatment to slow progression in secondary progressive MS.	Comment noted. See response to comment on Innovation by Association of British Neurologists.
	MS Trust	Yes, siponimod is the first drug to show a reduction in disability progression in 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. Drug treatment will be one element in the holistic management of progressive MS. 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.	Comment noted. See response to comment on Innovation by Association of British Neurologists.
Questions for consultation	Association of British Neurologists	**Have all relevant comparators for siponimod been included in the scope?** Possibility of ocrelizumab – see above. **Which treatments are considered to be established clinical practice in the NHS for secondary progressive multiple sclerosis?** None licenced at present. **What proportion of people with secondary progressive multiple sclerosis no longer has relapses?**	Comment noted. See response to comment on Comparators by Association of British Neurologists. Comment noted. No action required.

		The transition between RRMS and SPMS is often unclear and there may be some overlap. It is unusual for patients with established SPMS to relapse. The EXPAND trial records a relapse rate of 0.16/yr in the placebo group **How should best supportive care be defined? Does this differ depending on whether the person has ongoing relapses or not?** Multi-disciplinary care with access to MS specialist consultant neurologist, clinical nurse specialist, physiotherapist, occupational therapist speech and language therapist, dietician, neuropsychology, bladder and bowel management team. **Are the outcomes listed appropriate?** Yes with addition of MRI activity. **Are there any subgroups of people in whom siponimod is expected to be more clinically effective and cost effective or other groups that should be examined separately?** No. **Where do you consider siponimod will fit into the existing NICE pathway, 'Multiple Sclerosis'?** A new section for Secondary Progressive MS is required. **NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on**	Comment noted. No action required. Comment noted. The composition of established clinical management will be considered during any appraisal of siponimod. Comment noted. See response to comment on Outcomes by Association of British Neurologists. Comment noted. No action required. Comment noted. No action required.

		the appropriateness of appraising this topic through this process. Appropriate. **NICE has published an addendum to its guide to the methods of technology appraisal which states the methods to be used where a cost comparison case is made.** • **Would it be appropriate to use the cost comparison methodology for this topic?** Possibly ocrelizumab. • **Is the new technology likely to be similar in its clinical efficacy and resource use to any of the comparators?** Ocrelizumab • **Is the primary outcome that was measured in the trial or used to drive the model for the comparator(s) still clinically relevant?** The primary outcome of 3 month confirmed disability progression is still relevant but less so than 6 month confirmed disability progression (a secondary outcome)	Comment noted. No action required. Comment noted. See response to comment on Comparators by Association of British Neurologists. Comment noted. See response to comment on Comparators by Association of British Neurologists. Comment noted. The appropriateness of any outcome will be considered during any appraisal of siponimod.

		• **Is there any substantial new evidence for the comparator technology that has not been considered? Are there any important ongoing trials reporting in the next year?** No.	Comment noted. No action required.
	Novartis	**What proportion of people with secondary progressive multiple sclerosis no longer has relapses?** The distinction of people with SPMS with relapses and those without relapses is difficult to determine and the proportion has therefore not been reported consistently. **How should best supportive care be defined?** Best supportive care can be a combination of symptomatic treatment and/or neuro-rehabilitation. **Does this differ depending on whether the person has ongoing relapses or not?** The definition of best supportive care, including the type of treatments a patient will receive, is expected to differ from person to person on the basis of many factors, including patient-specific symptom burden. As commented in the Comparators section, a person with SPMS and ongoing relapses will likely continue DMT treatment in clinical practice, if the clinician believes they might derive some benefit from that continued treatment.	Comment noted. No action required. Comment noted. See response to comment on Comparators by Novartis. Comment noted. See response to comment on Comparators by Novartis.

		Are there any subgroups of people in whom siponimod is expected to be more clinically effective and cost effective or other groups that should be examined separately? This is currently being evaluated. **Where do you consider siponimod will fit into the existing NICE pathway, 'Multiple Sclerosis'?** Pending the outcome of the appraisal we envisage that siponimod will fit in the "Disease-modifying therapies for multiple sclerosis" section of the multiple sclerosis NICE pathway. **NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on the appropriateness of appraising this topic through this process. (Information on the Institute's Technology Appraisal processes is available at http://www.nice.org.uk/article/pmg19/chapter/1-Introduction).** The STA process is the appropriate route for the appraisal of siponimod.	Comment noted. No action required. Comment noted. No action required. Comment noted. No action required.
	MS Society	**To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly.** There is likely to be a high demand for siponimod, given it is the first treatment to significantly slow progression in secondary progressive MS. As increasing new treatments become available for progressive forms of MS, MS services face capacity and infrastructure challenges	Comment noted. No action required.

		in order to be able to prescribe, monitor and manage new patients who want these treatments. Services will have to adapt in order to meet the needs of this group who for the very first time have hope of an effective treatment to address progression. It is also the case that many people with progressive forms of MS, especially those living with the condition for many years, have fallen out of contact with specialist services over the years. The MS Society's My MS My Needs Survey in 2016 found that of those respondents with secondary progressive MS with relapses, 15% had not seen an MS specialist nurse in the past 12 months but needed to (it was 14% for those with secondary progressive and no relapses). In terms of access to neurologists, of those respondents with secondary progressive MS with relapses, 15% had not seen a neurologist in the past 12 months but needed to (it was 12% amongst those with secondary progressive with no relapses). MS services will need to be proactive in getting back in contact with patients with secondary progressive MS that could benefit from this treatment if they are to have the opportunity to access it, but understandably not all services will have the capacity to do so. However, there are examples of services that are already doing this that could look to be replicated, such as Northumbria Healthcare Community MS Specialist Nurse team. Reinstating contact with people with SPMS and MS services would have broader benefits to than just those delivered to patients by the treatment itself – effectively managing the needs of patients with progressive MS provides opportunities to intervene and refer to community support services	

		before needs escalate and in worse cases, result in unnecessary admissions to hospital. **Are there any subgroups of people in whom siponimod is expected to be more clinically effective and cost effective or other groups that should be examined separately?** This will be determined by the EMA licence wording of the licensed indication. However, the EXPAND trail included patients were aged 18-60 with no evidence of relapse up to 3 months before, EDSS of 3.0 to 6.5, and had disability progression in the two years before.	Comment noted. No action required.
	MS Trust	**Have all relevant comparators been included?** See our comments above. We anticipate that "best supportive care" will be a problematic comparator to quantify and will be very unlikely to reflect the true availability of services to people with secondary progressive MS. To properly reflect the current cost to the NHS of treatments taken by people with secondary progressive MS, this appraisal must recognise that all of the disease modifying drugs continue to be used at least up until an established EDSS 7, even though this use is not strictly covered by licensing. As a minimum, a blended comparator of disease modifying drugs based on UK market share should be used. **Which treatments are considered to be established clinical practice in the NHS for SPMS?**	Comment noted. See response to comment on Comparators by Novartis.

		See our comments above. Because there are no treatments for secondary progressive MS, clinicians delay diagnosis and continue to prescribe all of the disease modifying drugs beyond the transition from relapsing remitting to secondary progressive MS. For an accurate picture of the true cost to the NHS of treating secondary progressive MS, this appraisal must recognise that all of the disease modifying drugs continue to be used at least up until established EDSS 7. As a minimum, a blended comparator of disease modifying drugs based on UK market share should be used. Management of SPMS focuses on four key areas: symptom management; prevention of complications; maintaining function and promoting general health and wellbeing. **What proportion of people with SPMS no longer has relapses?** We are not aware of studies which report this. Recent research indicates that relapse occurrence decreases with patient age . Research by Confavreux et al (2000) established that relapses do not significantly influence the progression of irreversible disability . **How should best supportive care be defined? Does this differ depending on whether the person has ongoing relapses or not?** See our comments above. Management of secondary progressive MS focuses on four key areas: symptom management; prevention of	Comment noted. See response to comment on Comparators by Novartis. Comment noted. No action required.

		complications; maintaining function and promoting general health and wellbeing. As noted above, during the transition from relapsing to secondary progressive MS, patients may continue to take one of the disease modifying drugs; the NHSE treatment algorithm for MS disease-modifying therapies lists stopping criteria which includes EDSS of 7.0 persistent for more than 6 months due to MS. **Are the outcomes listed appropriate?** See our comments above. **Are there any subgroups of people in whom siponimod is expected to be more clinically effective and cost effective or other groups that should be examined separately?** It is anticipated that the licence will include all people with secondary progressive MS, both relapsing and non-relapsing. The wording of the licensed indication may specify subgroups of patients with secondary progressive MS most likely to benefit from siponimod treatment. In the EXPAND phase III study, patients were aged 18-60, had EDSS of 3.0 to 6.5, disability progression in the two years before the study and no evidence of relapse in the 3 months before randomisation. The study analysed data for several subgroups: • presence or absence of relapses in the 2 years before randomisation	Comment noted. See response to comment on Comparators by Novartis. Comment noted. No action required.

		• rapid progression (increase in EDSS of at least 1.5 points in 2 years before randomisation • Multiple Sclerosis Severity Score of 4 or more at baseline. **Where do you consider siponimod will fit into the existing NICE pathway Multiple Sclerosis?** We would expect siponimod to be offered as soon as possible after diagnosis of secondary progressive MS or earlier during the transition from relapsing and secondary progressive MS. **Do you consider siponimod to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way the current need is met (step-change)?** See our comments above. **Do you consider that the use of siponimod can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?** 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 secondary progressive MS would similarly result in a greater focus on services for progressive MS and a more pro-active approach to managing secondary progressive MS which would ultimately benefit a	Comment noted. No action required. Comment noted. See response to comment on Innovation by Association of British Neurologists.

		much wider group of people with secondary progressive MS than just those who might be eligible for siponimod. **To help NICE prioritise topics for additional adoption support, do you consider there will there be any barriers to adoption of this technology into practice?** We are not aware of any additional NICE Guidelines or Technology Appraisals which might be necessary to allow the adoption of siponimod as a treatment for secondary progressive MS. MS services are likely to be overstretched by demand for the first treatment for secondary progressive MS; at the earliest opportunity it will be important to communicate eligibility criteria and manage expectations. MS services will also need to consider reinstating contact with patients who have been discharged from neurological services.	Comment noted. No action required.

Comment 3: provisional matrix of consultees and commentators

Section	Consultee/ Commentator	Comments [sic]	Action
Provisional matrix	Novartis	Betaferon is not recommended by NICE for multiple sclerosis (TA527) and Novartis therefore questions whether it is appropriate to list Bayer as a possible comparator company.	Comment noted. The economic analysis section states that the availability and cost of biosimilars should be taken into account; therefore, we have included the manufacturer of Betaferon. No action required.