National Institute for Health and Care Excellence

Health Technology Evaluation

Tolebrutinib for treating non-relapsing secondary progressive multiple sclerosis ID6351
Response to stakeholder organisation comments on the draft remit and draft scope

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Comment 1: the draft remit and proposed process

Section	Stakeholder	Comments [sic]	Action
Appropriateness of an evaluation and proposed evaluation route	Sanofi	Sanofi agrees that single technology appraisal is the appropriate route.	Thank you for your comment.
	MS Society	We agree that NICE should appraise the clinical and cost effectiveness of tolebrutinib for non-relapsing secondary progressive multiple sclerosis. We also agree that it is appropriate that NICE evaluate this technology through its Single Technology Appraisal process.	Thank you for your comment.
	MS Trust	The STA is an appropriate methodology for this appraisal.	Thank you for your comment.
	Association of British Neurologists	A single technology appraisal of tolebrutinib for treating secondary progressive multiple sclerosis is proposed. There are precedents for this approach from NICE evaluations of other disease modifying therapies noting that, in this case, there are no direct comparator disease modifying therapies; there are no disease modifying	Thank you for your comment.

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		therapies available for people with non-relapsing secondary progressive multiple sclerosis currently. There is a very significant unmet need for treatment for non-relapsing secondary progressive multiple sclerosis; there are no currently available treatments for this patient population who have a high disability burden. Tolebrutinib is a Bruton kinase inhibitor which is a new class of drug for the treatment of multiple sclerosis.	
Wording	Sanofi	Yes. However, we believe the title of the appraisal should be modified to reflect the anticipated population within the marketing authorisation: “Tolebrutinib for treating non-relapsing secondary progressive multiple sclerosis ID6351”.	Thank you for your comment. The title will be updated.
	MS Society	Yes.	Thank you for your comment.
	Association of British Neurologists	Remit: To appraise the clinical and cost effectiveness of tolebrutinib within its marketing authorisation for treating non-relapsing secondary progressive multiple sclerosis. This is considered appropriate assuming a marketing authorisation will be granted (not in place at the time of writing)	Thank you for your comment.
Timing Issues	Sanofi	None.	Thank you for your comment.
	MS Society	Currently there are no disease modifying therapies available to people with non-relapsing secondary progressive MS, making this appraisal incredibly urgent to the NHS. People with secondary progressive MS experience worsening disability and symptoms but have fewer treatment options.	Thank you for your comment.

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		Furthermore, many are not receiving the recommended non-DMT clinical management.	
	Association of British Neurologists	Given the current lack of alternative disease modifying therapies for people with non-relapsing secondary progressive multiple and associated unmet clinical need, combined with high profile coverage of positive clinical trial data, it is anticipated that there will be significant demand for tolebrutinib. We support urgent review such that NICE's decision regarding clinical and cost effectiveness of tolebrutinib is available as soon as possible following anticipated marketing authorisation.	Thank you for your comment.
Additional comments on the draft remit	Sanofi	N/A	Thank you for your comment.
	MS Trust	The paperwork pack for STA ID6351 references secondary progressive MS, but the web page says multiple sclerosis (relapsing).	Thank you for your comment. NICE will ensure that any web pages reflect the appropriate secondary progressive multiple sclerosis wording.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Sanofi	We believe the background requires more clarity on the nature of secondary progressive multiple sclerosis (SPMS). Most patients diagnosed with multiple sclerosis (MS) have an underlying disease process called smouldering disease.	Thank you for your comment. The background information has been updated to clarify the definition of

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		Smouldering neuroinflammation is an umbrella term for the chronic neuroinflammation seen in MS that is associated with the neurodegeneration and disability accumulation seen as MS progresses.[1-5] Initial manifestation of this chronic neuroinflammation can begin before the onset of clinical symptoms across the MS spectrum and becomes a progressively prominent driver of disability accumulation over time, independently of relapse-associated worsening. MS can therefore be considered a disease continuum with a predominant relapsing–remitting course to begin with and then secondary progressive disease being dominated by smouldering neuroinflammation later in the disease course.[4, 6-9] In addition, the definition of non-relapsing secondary progressive multiple sclerosis (nrSPMS) in the draft scope is incorrect and potentially misleading. In the draft scope it is stated that "Some people with secondary progressive multiple sclerosis have active or relapsing disease. Others experience continuing disability progression without further relapses. This is referred to as non-relapsing (non-active) secondary progressive multiple sclerosis". However, nrSPMS can include both patients with non-active disease and patients with active disease reflected in inflammatory changes visible on a magnetic resonance imaging (MRI). We suggest providing a clear definition of the overlap between active and non-relapsing disease in the context of SPMS[3, 10, 11] : • SPMS occurs in people following an initial diagnosis of relapsing–remitting MS (RRMS), but at this point the disease is dominated by progressive accumulation of disability, with or without occasional relapses, inflammatory activity on MRI scans, minor remissions and plateaus	non-relapsing secondary progressive multiple sclerosis. The epidemiology figures for non-relapsing secondary progressive multiple sclerosis are from American and Danish databases and may not reflect the UK. The suggested wording for current treatment options has been adopted.

Section	Consultee/ Commentator	Comments [sic]	Action
		• Active SPMS: SPMS with relapses and/or evidence of new MRI activity • Non-active SPMS: continued progression without relapses or MRI activity • **nrSPMS** is defined by patients ceasing to experience confirmed relapses, but continuing to experience disability accumulation. These patients can present with inflammatory activity on an MRI scan but without relapse activity and be classed as having active nrSPMS, or only present with disability accumulation and be classed as having non-active nrSPMS[3] Regarding epidemiology of nrSPMS, people with nrSPMS may make up as much as 21% of the total MS population.[12, 13] Two recent retrospective real-world analyses using large databases examined the characteristics and prevalence of MS subtypes: the CLIMB study and DMSR study. These studies found that the proportion of people with the nrSPMS phenotype ranged between 18% and 21%.[12, 13] It is also likely that a proportion of patients with nrSPMS are currently not diagnosed with this phenotype, given the limited treatment options available. Considering the inclusion of patients with active nrSPMS within the nrSPMS population, it is incorrect to state “There are currently no disease-modifying therapies available for non-relapsing secondary progressive multiple sclerosis”. Siponimod is recommended by NICE in patients with active disease.[14] As a result a more accurate wording would be “There are currently no disease-modifying therapies recommended for the whole nrSPMS population”. There is also evidence that other disease modifying therapies are commonly used off-label in this patient population,[15] further highlighting the unmet need for treatment options targeted at nrSPMS.	

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	MS Society	1. The draft remit uses an outdated estimate of prevalence. Our current estimate based on 2024 research is that over 150,000 people have MS in the UK, including over 123,000 in England[1]. The source cited is correct, but the figure isn't. 2. Given the vast majority of people with relapsing remitting MS go on to develop secondary progressive MS, we think that this should be made clearer in the scope. The research cited in the background information also found that 93% of people diagnosed with relapsing remitting MS had progressed to secondary progressive at 30 years. 3. Evidence suggests that more people have non-relapsing SPMS than active SPMS[2]. Though a self-selecting sample, this is reflected in the respondents to our last My MS My Needs Survey[3].	Thank you for your comment. The figures and reference have been updated in line with the latest research. The scope has been updated to note that most people with RRMS go on to progress to SPMS.
	MS Trust	I feel that it's time we started referencing the current understanding of MS as being one condition with varying impact from inflammatory relapse activity and the progressive accumulation of disability over time. The statement as it stands is not wrong, but it implies separate and distinct disease states where individuals fall within a continuum.	Thank you for your comment. The scope has been updated to note that most people with RRMS go on to progress to SPMS.
	Association of British Neurologists	*Multiple sclerosis has an unpredictable course which varies in severity and rate of progression.* This statement is correct but ignores the important point that the majority of patients with MS will develop secondary progressive disease which is, by definition, associated with a decline in neurological function and accrual of disability. Suggest:	Thank you for your comment. The scope has been updated to: - note that most people with RRMS go on to progress to SPMS

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		The vast majority of people with multiple sclerosis will experience disease progression which is the major driver of disability, although this does vary in severity and rate of progression. *Symptoms can include pain, disturbance to muscle tone including weakness or spasticity, chronic fatigue, unsteady gait, speech problems, incontinence, visual disturbance, and cognitive impairment.* Weakness may, or may not, be related to altered tone and sensory symptoms are highly prevalent. Therefore suggest: 'Symptoms can include pain, sensory disturbance, limb weakness and gait impairment, spasticity, fatigue, inco-ordination, incontinence, speech problems, visual failure and cognitive impairment.' *Relapsing–remitting multiple sclerosis is the most common clinical form of multiple sclerosis.* This is not correct. Suggest: 'The majority of people with multiple sclerosis present with relapsing-remitting multiple sclerosis and the overwhelming majority of these will develop secondary progressive multiple sclerosis which is the most prevalent disease subtype.' Relapsing–remitting multiple sclerosis can progress to secondary progressive multiple sclerosis. Rather than 'can' progress, relapsing-remitting multiple sclerosis is highly likely to progress. Therefore suggest: 'With time, the majority of people with relapsing-remitting multiple sclerosis develop secondary progressive disease.' *Some people with secondary progressive multiple sclerosis have active or relapsing disease. Others experience continuing disability progression without*	- include the proposed updates to the list of symptoms - remove the statement that RRMS is the most common clinical form of MS - include the definition of active SPMS

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		further relapses. This is referred to as non-relapsing (non-active) secondary progressive multiple sclerosis. It may be helpful to clarify that 'active' multiple sclerosis may be defined clinically with relapses or by radiological evolution. Suggest: Secondary progressive multiple sclerosis with ongoing increase in disability is considered 'active' when associated with superimposed relapses and/or new radiological changes attributable to multiple sclerosis. This occurs in a minority and most people with secondary progressive multiple sclerosis experience continuing disability progression without relapses or acquisition of new imaging abnormalities.	
Population	Sanofi	Please see comments above regarding nrSPMS encompassing both active and non-active disease.	Thank you for your comment.
	MS Society	The population of people with non-relapsing secondary progressive MS is defined appropriately.	Thank you for your comment.
	MS Trust	Current population estimates are now 150,000 pwMS in the UK. The oft-used stat about the percentage of people with RRMS transitioning to SPMS after 20 yrs is incomplete without a sense of the proportion who will eventually get an SPMS diagnosis. This is a single point in a long journey.	Thank you for your comment. The figures have been updated in line with the latest research. We have also added the percentage of people who progress from RRMS to SPMS at 30 years.

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	Association of British Neurologists	Yes	Thank you for your comment.
Subgroups	Sanofi	Tolebrutinib should be considered for the entire nrSPMS population.	Thank you for your comment. Subgroups have been specified for people with and without MRI evidence of disease activity based on the comments that siponimod is a relevant comparator for people with active disease.
	MS Society	We don't propose any subgroups.	Thank you for your comment. Subgroups have been specified for people with and without MRI evidence of disease activity based on the comments that siponimod is a relevant comparator for people with active disease.
	Association of British Neurologists	No subgroups are specified. The relevant phase III clinical trial included people with non-relapsing secondary progressive multiple sclerosis aged 18-60 years who had not had	Thank you for your comment. Subgroups have been specified for people with and without

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		relapses in the preceding 24 months, had evidence of clinical progression in preceding 12 months and who had an EDSS score of 3-6.5. Multiple sclerosis is more common in female patients and there should be specific consideration of people who are considering pregnancy, and those who are pregnant or breastfeeding. The burden of safety monitoring on those who are disabled and/or live remotely from specialist centres should be considered. The implications of drug-switching for those on disease modifying therapy for relapsing-remitting multiple sclerosis should be considered.	MRI evidence of disease activity based on the comments that siponimod is a relevant comparator for people with active disease. The committee will consider these points during the appraisal (please see the equality section and the equality impact assessment).
Comparators	Sanofi	The current management of nrSPMS comprises: • Siponimod in patients with active disease[14] • Other disease modifying therapies that are commonly used off-label in this patient population[15] • Symptomatic treatments including drugs (for example to relieve spasticity and fatigue), as well as specialist support including physiotherapy, or occupational therapy[16]	Thank you for your comment. The comparators have been updated to: Established clinical management without tolebrutinib, including but not limited to: Siponimod (for people with active non-relapsing secondary progressive multiple sclerosis) Best supportive care

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	MS Society	The listed comparator is the only option recommended by NICE for people with non-relapsing secondary progressive MS. However, the committee must recognise that many people with secondary progressive MS are not receiving optimum clinical management. 1. Many people with secondary progressive MS are not receiving recommended clinical care, including annual comprehensive reviews with specialists, coordinated care and access to symptom management and rehabilitation, as per NICE guidelines for management of MS. Too often, clinical services focus on those already on disease modifying therapies (DMTs) and therefore already 'known' to services. MS service resources are diverted away from advanced MS due to the demands of safely prescribing and monitoring people on DMTs[4].This means that people with secondary progressive MS are often 'lost' to services once DMT prescribing ends (or they were never on consultants' lists) and are less likely to have annual reviews[5] or have been able to see a neurologist when they needed to[6], compared to people with relapsing remitting MS. 2. Even if people with secondary progressive MS are known to clinical services, the existence, quality, proximity and capacity of services for symptom management and support to self-manage varies across the country. Services are overstretched and there is huge unmet need. For example, our last My MS My Needs survey showed that 40% people hadn't received specialist continence support they identified needing in the 12 months prior, 38% hadn't received physiotherapy they needed, and 84% hadn't received cognitive support they needed[7].	Thank you for your comment. The committee will consider these points during the appraisal.

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		3. Finally, in practice, some people with secondary progressive MS will continue being prescribed disease modifying therapies licensed for relapsing remitting MS. This is in part due to clinicians' reluctance to diagnose secondary progressive MS due to the limited treatment options.	
	Association of British Neurologists	There are no currently available disease modifying therapies for non-relapsing secondary progressive multiple sclerosis so current best standard of care (symptomatic management) would be appropriate. In addition, siponimod could be a comparator for those switched from a disease modifying agent for relapsing remitting multiple sclerosis following development of progressive disease without relapse or radiological disease activity.	Thank you for your comment. The comparators have been updated to: Established clinical management without tolebrutinib, including but not limited to: Siponimod (for people with active non-relapsing secondary progressive multiple sclerosis) Best supportive care
Outcomes	Sanofi	We believe that: • Relapse rate is not relevant, given the population is defined as non-relapsing SMPS • Severity of relapse is not relevant, given the population is defined as non-relapsing SMPS • Confirmed disability progression (CDP, defined as an increase of ≥ 1.0 point from the baseline Expanded Disability Status Scale [EDSS] score when the baseline score is ≤ 5.0, or an increase of ≥ 0.5 point	Thank you for your comment. Relapse-related outcomes have been removed from the scope and 'disability progression' has been added.

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		when the baseline EDSS score is > 5.0) and confirmed disability improvement (CDI, defined as a ≥1.0 point decrease on the EDSS score from baseline confirmed over at least 6 months) should be used instead of “disease progression”	
	MS Society	1. A wide variety of outcomes are important to people with MS, which may not be covered in health related quality of life measures. These include people’s ability to live independently, participate in social activities, and remain in work should they wish to. 2. We weren’t sure why three of the outcomes listed relate to relapses/disease activity when the population is for adults with non-relapsing secondary progressive multiple sclerosis.	Thank you for your comment. Relapse-related outcomes have been removed from the scope.
	MS Trust	Not sure why relapses and relapse severity are listed as outcomes for a non-relapsing subgroup of the SPMS population. For this population, I would want to see disability measures including upper body disability and cognition, as these are normally more granular at this point in an MS journey.	Thank you for your comment. Relapse-related outcomes have been removed from the scope.
	Association of British Neurologists	These are appropriate but will require clarification regarding the most appropriate metrics.	Thank you for your comment.
Equality	Sanofi	Recommending tolebrutinib for routine commissioning as a once-daily oral medication that can delay onset of disability accumulation and prevent symptoms can provide equality advantages for people with nrSPMS, especially prominent in those with severe disability. People with nrSPMS may require in-person appointments to take off-label medications or undergo therapy, which can be difficult to access for those with higher EDSS, EDSS ≥	Thank you for your comment. The committee will consider these points during the appraisal.

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		5.5, which is a disability severe enough to prevent full daily activities and the ability to walk 100 metres without aid or rest. This level of disability may require specialist transport, extensive travel and help from carers to access appointments. As an oral medication, tolebrutinib can easily be taken at home, compared with other medications, and can reduce the need to attend these appointments. In addition, the lack of requirement for an MRI scan at baseline can facilitate faster initiation of treatment.	
	MS Society	1. Any inequalities in access to the services in the pathway will result in inequalities in access to this treatment. This is particularly pertinent given that many people with secondary progressive MS are not part of existing MS team case lists, and there is an uneven distribution of sites prescribing disease modifying therapies across the country. 2. Access and take up of existing disease modifying therapies varies with ethnicity. There is a growing body of evidence that people with MS from non-white backgrounds are more likely to decline DMTs, less likely to start any DMTs and high-efficacy DMTs, and more likely to experience a delay in starting DMTs[8]. **3.** It could be harder for people with higher level of disability to access the treatment due to barriers they face travelling for healthcare. Even if the treatment is self-administered, there will be initiation and monitoring requirements of the treatment.	Thank you for your comment. The committee will consider these points during the appraisal.
	MS Trust	Being aware that women make up around 2/3rd of the MS population, downplaying their experiences and the significance of their disabilities could be considered sexist.	Thank you for your comment. The committee will consider these points during the appraisal.

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	Association of British Neurologists	Consideration will need to be given to those who are considering pregnancy, and those who either are pregnant or breast-feeding. The burden of safety monitoring on those who are disabled and/or live remotely from specialist centres should be considered. That tolebrutinib is an oral therapy has potential advantages in terms of hospital visits. Black and ethnic minority people with multiple sclerosis are more than twice as likely to transition to secondary progressive multiple sclerosis, even after controlling for socioeconomic status; this group is therefore more likely to be disproportionately affected by the lack of licensed disease modifying therapy for non-relapsing secondary progressive multiple sclerosis. [Langer-Gould AM, Gonzales EG, Smith JB, Li BH, Nelson LM. Racial and Ethnic Disparities in Multiple Sclerosis Prevalence. Neurology. 2022 May 3;98(18):e1818-e1827]	Thank you for your comment. The committee will consider these points during the appraisal.
Other considerations	Sanofi	None.	Thank you for your comment.
	MS Society	The evaluation should consider what's needed to ensure equitable access to tolebrutinib, should it be recommended. On top of the previous equality concerns, it should take into account: • that many people with secondary progressive MS aren't known to clinical services and the need to identify people who could benefit from the treatment • that deprivation negatively impacts access to existing disease modifying therapies[9]	Thank you for your comment. The committee will consider these points during the appraisal.

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		• how monitoring can occur as close to home as possible, given the numerous barriers people with secondary progressive MS face travelling. These include cost, poor disabled access on public transport, limited mobility, and symptoms such as fatigue, weakness and heat sensitivity.	
	Association of British Neurologists	A significant proportion of people with secondary progressive multiple sclerosis will not have active follow up in secondary care and are untreated and unmonitored despite acquiring disability over time. Given that there are no disease modifying therapy options for people with non-relapsing progressive multiple sclerosis, this appraisal addresses a significant unmet need; tolebrutinib, if licensed, offers a unique opportunity to re-engage and treat this underserved group. Given that disability is the major driver of multiple sclerosis-related costs (both direct (healthcare) and indirect (loss of productivity, social care), even modest delays to disability progression translate to major savings. Processes to minimise risk of tolebrutinib-associated liver disease will be required and the impact of these should be assessed. The paucity of real-world data and longer term follow up regarding disability outcomes should be noted.	Thank you for your comment. The committee will consider these points during the appraisal.
Questions for consultation	Sanofi	**Where do you consider tolebrutinib will fit into the existing care pathway for non-relapsing secondary progressive multiple sclerosis?** As an alternative to current treatments, as outlined above in the comparators section. **Is the population – adults with non-relapsing secondary progressive multiple sclerosis – appropriate for tolebrutinib?** Yes – as noted above this includes patients with active nrSPMS as defined as inflammatory activity on MRI and patients with non-active nrSPMS.	Thank you for your comment.

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		Should any other populations be considered? No. **What proportion of people with secondary progressive multiple sclerosis have non-relapsing disease?** People with nrSPMS may make up as much as 21% of the total MS population. Two recent retrospective real-world analyses using large databases examined the characteristics and prevalence of MS subtypes: the CLIMB study and DMSR study. These studies found that the proportion of people with the nrSPMS phenotype ranged between 18% and 21%.[12, 13] **What is established clinical management for non-relapsing secondary progressive multiple sclerosis?** The current management of nrSPMS consists of established clinical management including: Symptomatic treatments including drugs (for example to relieve spasticity and fatigue), as well as specialist support including physiotherapy, or occupational therapy[16] Patients with nrSPMS also frequently receive off-label disease modifying therapies that are commonly used in the wider MS population [12, 13, 15] Patients with active nrSPMS may also be able to receive: Siponimod in patients with active disease confirmed by MRI[16] **What do you expect the comparators to be for tolebrutinib for non-relapsing secondary progressive multiple sclerosis?** Current management, as described above. **Please select from the following, will tolebrutinib be:** C. Prescribed in secondary care with routine follow-up in secondary care	

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		Would tolebrutinib be a candidate for managed access? Sanofi believes tolebrutinib is suitable for routine commissioning for all eligible patients. Sanofi is committed to bringing tolebrutinib to patients and is open to conversations regarding managed access if required. **Do you consider that the use of tolebrutinib can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation?** Sanofi expects there are several benefits that are unlikely to be included in the quality-adjusted life year (QALY), as little data quantifying these impacts are available. These are however of high relevance to patients, caregivers and the broader healthcare system and include: • Improved access to treatment due to oral route of administration • Maintaining independence due to delayed disability • Full impact on the caregiver • Impact on employment, including through presenteeism and absenteeism • Potential reduction in long-term NHS and social care resource use	
	MS Society	The UK MS Register can offer useful data to support the evaluation, including clinical data on diagnosis and various self-reported measures from people with MS: • EQ5D-3L • Hospital Anxiety and Depression Score • Fatigue Severity Scale • MS Impact Scale Data from the Octopus trial on progressive MS will be coming into the Register database and will contain quality of life data.	Thank you for your comment.

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	MS Trust	These are important considerations, and would add consideration of monitoring requirements, location of prescribing service, given higher likelihood of disability including to mobility, fatigue and cognitive function at this point.	Thank you for your comment.
Additional comments on the draft scope	Sanofi	N/A	Thank you for your comment.
	Association of British Neurologists	What proportion of people with secondary progressive multiple sclerosis have non-relapsing disease? Approximately 75% people with multiple sclerosis will develop secondary progressive multiple sclerosis and the majority will have non-relapsing disease (approximately 3-5% will have active secondary progressive multiple sclerosis). However, it should be noted that multiple sclerosis is a spectrum (rather than presenting as distinct clinical phenotypes) and there has been a historical reluctance to diagnose secondary progressive disease given that treatment options have been more limited. What is established clinical management for non-relapsing secondary progressive multiple sclerosis? There are no disease modifying therapies for this population, although people who transition from relapsing remitting multiple sclerosis to a progressive phenotype who are on a current disease modifying treatment, can be treated with siponimod in the absence of relapses or radiological disease activity. Otherwise, only symptomatic treatments are available e.g. treatments for spasticity, pain, urinary symptoms etc. Please select from the following, will tolebrutinib be:	Thank you for your comment.

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		A. Prescribed in primary care with routine follow-up in primary care B. Prescribed in secondary care with routine follow-up in primary care C. Prescribed in secondary care with routine follow-up in secondary care D. Other (please give details): For comparators and subsequent treatments, please detail if the setting for prescribing and routine follow-up differs from the intervention. C Would tolebrutinib be a candidate for managed access? No	

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