National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Laquinimod for treating relapsing-remitting multiple sclerosis

Response to consultee and commentator comments on the draft scope

Section	Consultees	Comments	Action
Background information	Association of British Neurologists	We do not believe it is correct to say that "SPMS is characterised by gradually more or worsening symptoms with fewer, briefer remissions and a progressive increase in disability" [there are no remissions from the progressive disability that characterises and defines SPMS]; the phrase "SPMS is characterised by more persistent or gradually progressive increase in disability" would be more accurate. It should also be clear that MS not only "occurs when the body's immune system attacks myelin, a protective sheath around nerve fibres in the brain and spinal cord", but that it is also a neurodegenerative disease from its first manifestations. We suggest as sentence along the lines of: "Multiple sclerosis is a chronic, neurodegenerative disorder with multifocal inflammatory demyelination affecting the brain, optic nerves, and spinal cord and this process commonly leads to progressive neurological impairment and severe disability."	Comment noted. The background section has been updated.
	MS Trust	Background information does not capture the impact of MS on work and family life. People with MS are commonly diagnosed between the ages of 20 and 40 and may live with MS for 30-40 years. The variable nature of MS means that people given a diagnosis of MS and their families face many years of uncertainty. The disease can have a significant impact on work and family life, both for the individual and for informal carers.	Comment noted. Please note that the background section is only intended to provide a brief overview of the disease and its associated management.
	Novartis	No comments	Comment noted. No action required.
	Royal College of Nursing	NICE recommends fingolimod as an oral treatment for multiple sclerosis but access is variable across the four countries.	Comment noted. Please note that the background section is only intended to provide a

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		It's considered a second line escalation therapy for most centres and will only be prescribed in specialist units.	brief overview of the disease and its associated management. Consideration of uptake of the guidance is not part of the Appraisal Committee's remit.
	United Kingdom Clinical Pharmacy Association	The group considers the information accurate and complete for the purpose of the document.	Comment noted. No action required.
The technology/ intervention	Association of British Neurologists	Yes	Comment noted. No action required.
	Novartis	No comments	Comment noted. No action required.
	Royal College of Nursing	Yes	Comment noted. No action required.
	Royal College of Pathologists	The phrase "directly modulates the central nervous system resident parenchymal cells" is not quite accurate. Laquinimod is a novel immunomodulator, with both anti-inflammatory and neuroprotective properties.	Comments noted. The technology section has been updated.
	Teva UK	Accuracy would be enhanced by specifying as follows at the end of para 1, page 2: It is administered orally once daily.	Comment noted. Please note that the technology section is only intended to provide a brief overview. The manufacturer will need to provide further detail about the technology in its evidence submission.

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	United Kingdom Clinical Pharmacy Association	The group considers the description of the technology accurate.	Comment noted. No action required.
Population	Association of British Neurologists	The population is defined appropriately. Patient populations that should be considered separately include [1] previously untreated RRMS patients, [2] people with RRMS who have proved intolerant of, or unresponsive to, previous DMT, and [3] patients with highly active and rapidly evolving RRMS.	Comments noted. Consistent with other recent NICE single technology appraisals of treatments for relapsing-remitting multiple sclerosis, subgroups of patients will be considered if the evidence allows. See the 'other considerations' section of the scope.
	MS Society	The population is also likely to include the following groups and they should be considered as sub groups if the evidence allows: (1) People with relapsing-remitting MS who have had prior treatment for MS but treatment failed due to a lack of tolerability or efficacy. It will be important to specify the reasons for failed treatment i.e. 'unchanged or increased relapse rate or ongoing severe relapses compared with the previous year despite treatment with beta interferon'. (2) People who have not tolerated other therapies.	Comments noted. Consistent with other recent NICE single technology appraisals of treatments for relapsing-remitting multiple sclerosis, the subgroups of patients listed will be considered if the evidence allows. The subgroups listed provide the manufacturer the flexibility to present evidence for people with relapsing-remitting multiple sclerosis whose disease has responded inadequately to prior disease modifying treatment or whose disease is intolerant to disease modifying treatment. See the 'other considerations'

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			section of the scope.
	MS Trust	Depending on marketing authorisation, the populations likely to be treated with laquinimod include treatment naïve, those who have not responded to prior disease modifying therapies (DMTs), those with intolerable side effects to DMTs. In clinical trials, laquinimod appears to have approximately equivalent efficacy at reducing relapse rates compared to current first line treatments (beta interferons and glatiramer acetate). Highly active RRMS and rapidly evolving severe RRMS are artificial subgroups defined for the purpose of drug licensing and are not a clinical subgroup. The published data does not include in-depth analysis of these sub-groups. We do not anticipate that laquinimod would be used an alternative to fingolimod or natalizumab which are licensed to treat these subgroups.	Comments noted. Consistent with other recent NICE single technology appraisals of treatments for relapsing-remitting multiple sclerosis, the subgroups of patients listed will be considered if the evidence allows. The subgroups listed provide the manufacturer the flexibility to present evidence for people with relapsing-remitting multiple sclerosis whose disease has responded inadequately to prior disease modifying treatment or whose disease is intolerant to disease modifying treatment. See the 'other considerations' section of the scope.
	Novartis	No comments	Comment noted. No action required.
	Royal College of Nursing	Will this be first or second line treatment? Will this be first or second line treatment? Adolescents with MS and Paediatric MS should be considered.	Comments noted. The recommendations made by NICE will be based on the assessment of the clinical and cost effectiveness of the technology within its licensed indication for treating multiple sclerosis.
	Royal College of	Data from the two phase-3 studies of laquinimod — Assessment of Oral	Comments noted. The

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	Pathologists	Laquinimod in Preventing Progression in Multiple Sclerosis (ALLEGRO) and BRAVO — presented at the 29th Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) suggest that laquinimod may have an effect on disability in patients with MS not related to its effect on relapse rate and inflammation; a relative reduction of 30% in 3-month disability progression, 6 times greater than predicted by the inflammatory data. The neuroprotection property of Laquinimod seems to be independent of its anti-inflammatory effect. If the drug can reduce disability independent of relapse/inflammation, it may work in the secondary progression phase of the disease where disability is independent of attacks. Data from the ALLEGRO study suggest that early treatment with laquinimod demonstrated significant benefit in terms of slowing disability progression compared to delayed treatment.	recommendations made by NICE will be based on the assessment of the clinical and cost effectiveness of the technology within its licensed indication for treating multiple sclerosis.
	Teva UK	Although the broad population is appropriately defined, some of the subgroups as indicated by the current list of comparators are not appropriate (see comments in 'Comparators' section below).	Comments noted. Subgroups of patients will be considered if the evidence allows.
	United Kingdom Clinical Pharmacy Association	We noted that patients with RRMS who have received prior treatment will be considered. Clarification is required if that includes patients who • failed on treatment because of efficacy • failed on treatment because of tolerability • would prefer an oral treatment despite of being adequately controlled on current treatment.	Comments noted. Consistent with other recent NICE single technology appraisals of treatments for relapsing-remitting multiple sclerosis, the subgroups of patients listed will be considered if the evidence allows. The subgroups provide the manufacturer the flexibility to present evidence for people with relapsing-remitting multiple sclerosis whose disease has responded

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			inadequately to prior disease modifying treatment or whose disease is intolerant to disease modifying treatment. See the 'other considerations' section of the scope.
Comparators	Association of British Neurologists	Beta interferon and glatiramer acetacte are standard first line treatments and should be used as comparators, except for patients with rapidly evolving sever MS as defined in [3] above, where natalizumab and fingolimod would be the most appropriate comparators. No single one of these products could be described as 'best alternative care', but in combination, one or other of these agents would represent the best alternative for the majority of patients with RRMS. To include "best supportive care with no disease-modifying treatment" as a formal comparator does not reflect good (or defensible) clinical practice in the UK.	Comments noted. No action required.
	MS Society	The treatments listed are the standard treatments used in the NHS. However, Extavia is also routinely used as a treatment for MS but sits outside the risk-sharing scheme. This treatment should be brought within the scope of the appraisal. As laquinimod is likely to be first line treatment it should be compared with the mean cost and mean efficacy of current first line therapies including Extavia, glatiramer acetate and the risk-sharing scheme drugs.	Comments noted. The comparators have been updated. The manufacturer is expected to consider all formulations of beta interferons that are established NHS practice in England in its evidence submission. The scope identifies all potentially relevant comparators, taking into account issues likely to be considered by the Appraisal Committee when selecting the most appropriate comparator. At this stage of the appraisal, identification of comparators

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			should be inclusive of all available options. When selecting the most appropriate comparator(s), the Committee will consider: • established NHS practice in England. • the natural history of the condition without suitable treatment. • existing NICE guidance. • cost effectiveness. • the licensing status of the comparator.
	MS Trust	The MS Trust notes that best supportive care is not listed as a comparator (cf draft scope for dimethyl fumarate and teriflunomide). However the topic of best supportive care is raised under questions for consultation - our response to this is given below. We note the addition of further comparators in the October 2013 draft scope. While we recognise this may be appropriate for the sake of completeness, we believe there is insufficient evidence to directly compare laquinimod with dimethyl fumarate, teriflunomide, alemtuzumab, natalizumab or fingolimod. We do not anticipate that laquinimod would be used an alternative to fingolimod or natalizumab.	Comments noted. The comparators have been updated. The scope identifies all potentially relevant comparators, taking into account issues likely to be considered by the Appraisal Committee when selecting the most appropriate comparator. At this stage of the appraisal, identification of comparators should be inclusive of all available options.
	Novartis	NICE has proposed that fingolimod should be a comparator for laquinimod. This proposal is not appropriate.	Comments noted. The comparators have been updated.

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		Fingolimod is licensed and approved by NICE for patients with highly active relapsing remitting MS (RRMS). We have found no evidence which indicates that laquinimod will be licensed, or will have available data, in this MS sub-population. A recent Cochrane review (He, Han et al 2013) found only one study which matched its criteria: Comi, Jeffery et al (2012) which is identified by the Cochrane review as presenting a high risk for attrition bias due to drop outs. Neither the Cochrane review nor Comi, Jeffery et al (2012) makes reference to highly active disease. In the latter publication, sub-group analysis could not be performed as planned. Since the licence for laquinimod is unlikely to specify highly active RRMS and there will be little evidence to support a comparison of its use in this population with fingolimod, it is difficult to justify a rationale for including fingolimod as a comparator. Therefore, fingolimod should be removed from the scope. He D, Han K, Gao X, Dong S, Chu L, Feng Z, Wu S (2013) "Laquinimod for multiple sclerosis (Review)" Cochrane Collaboration Issue 8 Comi G, Jeffery D, Kappos L, Montalban X, Boyko A, Rocca M, Filippi M (2012) "Placebo-Controlled Trial of Oral Laquinimod for Multiple Sclerosis" N Engl J Med 2012;366:1000-9.	Consistent with recent NICE single technology appraisals of treatments for relapsing-remitting multiple sclerosis, subgroups of patients will be considered if the evidence allows. The scope identifies all potentially relevant comparators, taking into account issues likely to be considered by the Appraisal Committee when selecting the most appropriate comparator. At this stage of the appraisal, identification of comparators should be inclusive of all available options. When selecting the most appropriate comparator(s), the Committee will consider: • established NHS practice in England. • the natural history of the condition without suitable treatment. • existing NICE guidance. • cost effectiveness. • the licensing status of the comparator.
	Royal College of Nursing	The comparators are a mix of first and second line treatment escalation options and may not represent an authentic spectrum of the treatment options for MS.	Comments noted. The comparators have been

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			updated. Please note NICE can only appraise technologies within their licensed indications. The scope identifies all potentially relevant comparators, taking into account issues likely to be considered by the Appraisal Committee when selecting the most appropriate comparator. At this stage of the appraisal, identification of comparators should be inclusive of all available options. When selecting the most appropriate comparator(s), the Committee will consider: • established NHS practice in England. • the natural history of the condition without suitable treatment. • existing NICE guidance. • cost effectiveness. • the licensing status of the comparator.
	Teva UK	The beta interferons and glatiramer acetate are the standard treatments currently used in the NHS to manage multiple sclerosis (MS), and are appropriate for comparison with laquinimod. Natalizumab and fingolimod are indicated in highly active and rapidly evolving	Comment noted. The comparators have been updated. The scope identifies all potentially relevant

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		severe (RES) relapsing remitting multiple sclerosis patient populations – populations that do not appear to have been represented in the laquinimod clinical trials programme. These would therefore not be appropriate comparators. Both phase III laquinimod studies (ALLEGRO and BRAVO) were placebo controlled. BRAVO included interferon beta-1a i.m. as an active comparator arm and therefore patients with prior use of interferon were excluded. In ALLEGRO approximately 1/3rd of patients reported prior interferon use. There were no subgroups in the pivotal studies meeting the definition: "Patients with high disease activity despite treatment with beta interferon. This group is defined as patients who have failed to respond to a full and adequate course of a beta interferon. Patients should have had at least one relapse in the previous year while on therapy, and have at least nine T2-hyperintensive lesions in cranial MRI or at least one gadolinium-enhancing lesion". Teriflunomide, and alemtuzumab, are subject to ongoing NICE technology appraisals, and at this time are not 'considered to be established clinical practice in the NHS for relapsing-remitting multiple sclerosis'. Dimethyl fumarate is not yet licensed in the UK. Were they all to be licensed and the subject of successful NICE appraisals by the end of the year, it would still not be possible to refer them as 'established clinical practice in the NHS', since it will take a variable period of time for any therapy to become established as such. Thus these therapies should also not be considered as appropriate comparators for laquinimod at this time.	comparators, taking into account issues likely to be considered by the Appraisal Committee when selecting the most appropriate comparator. At this stage of the appraisal, identification of comparators should be inclusive of all available options. When selecting the most appropriate comparator(s), the Committee will consider: • established NHS practice in England. • the natural history of the condition without suitable treatment. • existing NICE guidance. • cost effectiveness. • the licensing status of the comparator.
	United Kingdom Clinical Pharmacy Association	The list of comparators is complete in our view. We note that the comparators are now including the new treatments currently under NICE appraisal.	Comments noted. Please note the comparators have been updated.
Outcomes	Association of British Neurologists	Yes. The addition of MRI measures brain atrophy as a marker preservation of brain integrity may also be considered.	Comment noted. The inclusion of MRI outcomes was discussed in the scoping workshop. Consultees agreed

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			that the main outcomes of importance to patients with multiple sclerosis were captured following the addition of freedom of disease activity.
	MS Trust	Relapses have a significant impact on daily life eg work, family commitments, leisure activities. It is this aspect of relapse control which has greatest relevance to patients, rather than clinical measures. The outcome measures should reflect the wider social and economic impact of MS relapses eg days of work lost, change in employment status. Patient reported outcome measures PROMS shoud be included. There is no indication how severity of relapses would be measured. Symptoms of multiple sclerosis should reflect the list of symptoms given in the Background section. Disability progression is not included in the outcomes. Data on this outcome is being collected in current DMT clinical trials, although there has been variation in how this outcome has been measured. Also, two year trial data may not be a sufficiently long time-frame to give adequate confidence that this is a legitimate outcome for the DMTs. There is no indication how freedom from disease activity would be measured. This is a relatively new concept in DMT treatments and should not be included in appraisals until there is clinical consensus on what freedom from disease activity constitutes. Brain atrophy, which is a marker for disease progression, should be included.	Comments noted. The inclusion of MRI outcomes was discussed in the scoping workshop. Consultees agreed that the main outcomes of importance to patients with multiple sclerosis were captured following the addition of freedom of disease activity.

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	Novartis	No comments	Comment noted. No action required.
	Royal College of Nursing	Yes	Comment noted. No action required.
	Royal College of Pathologists	In the ALLEGRO study, laquinimod showed a 23% reduction in annual relapse rate (p=0.0024), along with a significant 36% reduction in the risk of confirmed disability progression, as measured by Expanded Disability Status Scale (EDSS) (p=0.0122). Treatment with laquinimod was also associated with a significant reduction in brain tissue loss, as measured by a 33% reduction in progression of brain atrophy (p<0.0001).	Comments noted. No action required.
	Teva UK	It is necessary to specify both 3- and 6-months disability progression as separate clinical outcomes. Sustained disability progression confirmed for 6 months is preferred by the European Medicines Agency in its guideline for the clinical investigation of medicinal products for the treatment of multiple sclerosis. Sustained disability progression confirmed for 6 months provides a more robust indication of the treatment effect when measuring disability progression. Would add an additional outcome in the form of brain atrophy. A reduction in brain atrophy represents the prevention of tissue injury and loss, and has been established as being correlated with neurological disability and neuropsychological impairment. Brain atrophy is being recognised as an increasingly relevant measure of disease progression in MS, and consequently also a measure of the efficacy of any given therapeutic intervention.	Comments noted. Within its evidence submission, the manufacturer is expected to present all results from the clinical trials that are relevant to the outcomes specified in the scope. The appropriateness of the results to the appraisal Committee's decision-making will then be considered at the first appraisal Committee meeting. The inclusion of MRI outcomes was discussed in the scoping workshop. Consultees agreed that the main outcomes of importance to patients with multiple sclerosis were captured following the addition of freedom of disease activity.
	United Kingdom	Yes.	Comment noted. No action

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	Clinical Pharmacy Association		required.
Economic analysis	Association of British Neurologists	No comments	Comment noted. 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 impact on a person's ability to remain in employment and on the levels of informal care they require. A recent report by the Work Foundation found that 80 per cent of PwMS (people with MS) stop working within 15 years of the onset of diagnosis and 44 per cent retire early because of the condition (Ready to Work? Meeting the Employment and Career Aspirations of People with Multiple Sclerosis, Bevan et al, The Work Foundation, 2011). The MS Society found 82 per cent of respondents in a 2010 survey had at some point during a relapse been unable to carry out their paid employment (A submission from the MS Society to inform the NICE appraisal of fingolimod for relapsing-remitting multiple sclerosis, 2010). Consequently the appraisal committee should take into account: - ability to remain in the workforce - stay in work or reduce absenteeism - independence for carers (The Work Foundation, 2011:4, report found that the "professional careers of 57 per cent of relatives are adversely affected by MS of a family member) - the value of informal care - the impact of informal care on carers - 87 per cent said caring for a family member or friend has had a negative impact on their mental health and 64 per cent carers blamed their poor health on a lack of practical support and 50 per cent on not enough financial support (In Sickness and in Health, Carers Week,	Comment noted. Costs will be considered from an NHS and Personal Social Services perspective.

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		2012). - reduction in social costs - increased tax revenue (Kennedy, 2009: 27) - cost of disability benefits It must be taken into account that MS is frequently a chronic progressive condition that has significant impact on the quality of life of individuals with the condition and also the lives of family members.	
	MS Trust	Economic analysis does not take into account the societal costs of relapses. Relapses have 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.	Comments noted. Costs will be considered from an NHS and Personal Social Services perspective.
	Novartis	No comments	Comment noted. No action required.
	Royal College of Nursing	Yes	Comment noted. No action required.
	United Kingdom Clinical Pharmacy Association	No comment	Comment noted. No action required.
Equality and Diversity	Association of British Neurologists	No age range is given in the description of 'Population(s)" relevant to this appraisal; we believe it will be necessary to be more explicit about whether the findings apply to children with RRMS (we believe children should be included).	Comments noted. The recommendations made by NICE will be based on the assessment of the clinical and cost effectiveness of the technology within its licensed indication for treating multiple sclerosis.
	Novartis	No comments	Comment noted. No action

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			required.
	Royal College of Nursing	See additional comments.	Comment noted. No action required.
	United Kingdom Clinical Pharmacy Association	No comment	Comment noted. No action required.
Innovation	Association of British Neurologists	This technology has the potential to make a significant (and positive) difference on the disease course of people with RRMS.	Comment noted. The potential innovative nature of the technology will be considered by the Appraisal Committee.
	MS Society	Currently there are no first line oral disease modifying treatment for relapsing-remitting forms of MS nor are there any treatments specifically indicated for SPMS with relapses; all available treaments are intravenous in their application. It is likely that laquinimod would present as a good alternative to injectible treatments as a first line treatment. The oral delivery of a treatment in the context of MS DMTs represents a significant innovation in the treatment of MS. It would dramatically increase the choice of treatments for those for whom the injectible DMTs would not be appropriate due to treatment failure, side-effects or indeed for those who do not want to self-inject. A report by the MS Society on oral therapies found that 95 per cent of people with MS would prefer to have their MS treatment administered via a pill (A submission fromt the MS Society to inform the NICE appraisal of fingolimod for relapsing-remitting multiple sclerosis, 2010). People with MS told us that injecting was uncomfortable, with many suffering complications from injection sites and 70 per cent suffering skin reactions. Many found that their MS symptoms exacerbated difficulties with injecting such as tremors and numbness of the hands. 72 per cent found self injecting difficult and needed to rely on others (MS Society, 2010). Laquinimod meets many of the health-related benefits criteria listed by Sir Ian Kennedy in 'Appraising the Value of Innovation and other benefits' (2009:24)	Comment noted. The potential innovative nature of the technology will be considered by the Appraisal Committee.

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		including: 1. The ability to offer a different mode of administering a drug - in this case, a tablet rather than an injection or infusion. 2. The opportunity to be treated at home rather than attend a hospital or clinic. 3. A reduction in unwanted side effects - current DMTs are a significant disruption to the daily lives of over 77 per cent of people affected by MS and in turn can impact on their employment. 4. Improvement in quality of life including enjoyment of greater dignity and independence – this treatment will give people with MS their family and, in some cases, their carers greater freedom. 5. The ability to minimise the social visibility of disease or care – a tablet can be taken more discretely and is less disruptive than infusions or injections. The current treatments for relapsing-remitting forms of MS are predominately administered by self-injection, with the exception of Fingolimod, which is a second line oral treatment. This lack of choice has a significant impact on PwMS both emotionally, physically and socially. This treatment will give people with MS a choice of an oral therapy, which would: - enable PwMS to continue everyday activities without planning their lives around their treatments and therapies - enable more independent living and improve lives of carers and families as well as PwMS - reduce stress and anxiety involved from daily or weekly injecting and overall emotional impact of injecting - added convenience and improved quality of life - lead to less dependence on familiy and carers - give people greater freedom particularly when planning travel. Current intravenous treatments need to be refrigerated and require administrative	

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		preparation when travelling abroad. In considering the value and innovation of an oral therapy, the inconvenience of injecting and/or going to hospital for infusions several times a week and the increased dependence a friend, family member or carer must be considered by the appraisal committee as well as people's ability to take an active role in society including employment and/or taking care of their family rather than being dependent on them. This is particularly important given that MS affects women and men at stages in their lives where they will possibly have young families.	
	MS Trust	Existing first-line disease modifying treatments are all injected; the specific benefits of an oral route of administration for should be taken into account. While laquinimod has a moderate effect on relapse rates, it has a siginifcant impact on brain atrophy and disability progression, suggesting a broader effect on underlying disease pathology than existing treatments. This different profile of activity represents a valuable addition to existing treatments for MS.	Comments noted. The potential innovative nature of the technology will be considered by the Appraisal Committee.
	Novartis	No comments	Comment noted. No action required.
	Royal College of Nursing	Yes, it offers far more choice to people with MS than they currently available. It has the capacity to improve the step wise/escalation treatment approach. It is innovative and could potentially enhance compliance, adherence and ultimately improve the patient experience.	Comments noted. The potential innovative nature of the technology will be considered by the Appraisal Committee.
	Royal College of Pathologists	It is innovative due to the following attributes: • Being oral medication • It is an immunomodulator, not immunosuppressive: cellular/humoral immune responses remain intact • It increases brain-derived neurotrophic factor: neuroprotection effect	Comments noted. The potential innovative nature of the technology will be considered by the Appraisal Committee.

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	Teva UK	Despite the availability of a range of DMTs, there are significant needs that are not fully met by current treatments. Laquinimod has a novel mechanism of action that offers CNS protection at least partially independent of its mode of action outside the CNS. Laquinimod mechanisms potentially associated with clinical efficacy include: • Preclinical evidence of laquinimod activity on CNS-resident immune cells implicated in MS pathology • Preclinical and *in vitro* evidence of laquinimod activity on peripherally initiated inflammation During its clinical development program, laquinimod demonstrated a consistent and significant effect on both brain atrophy and 3- and 6-month disability (i.e. outcomes consistent with neurodegenerative processes). With the prevention of disability emerging as the key clinical measure in the treatment of MS, a clinical data set that demonstrates significant effect on brain atrophy (a correlate of future physical disability and neuropsychological impairment) and on 3- and 6 month disability demonstrates both innovation and relevance to current and evolving clinical imperatives. Laquinimod has been shown to reduce the risk of disability progression to a far greater extent than predicted based on its effect on relapse, with that reduction in disability progression occurring regardless of relapse status.	Comments noted. The potential innovative nature of the technology will be considered by the Appraisal Committee.
	United Kingdom Clinical Pharmacy Association	The technology will increase the number of oral treatments available to MS patients. It is innovative in view of mode of action	Comments noted. The potential innovative nature of the technology will be considered by the Appraisal Committee.
Other considerations	Association of British Neurologists	None	Comment noted. No action required.

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	MS Trust	We are pleased that the four new DMTs (dimethyl fumarate, alemtuzumab, teriflunomide and laquinimod) are to be appraised as STAs as this will ensure timely appraisal of each of the treatments as soon as each is licensed. The terms of the licence granted to a drug will have an impact on the guidance issued by NICE. In MS, this has created de-facto patient sub-groups (eg highly active despite treatment or rapidly evolving severe) which may not reflect clinical reality or the true complexity of prescribing. There is considerable risk that this landscape could be further complicated as each of these four drugs goes through appraisal separately. First and second lines may not be easily demarcated. This could potentially be made worse by appraising the drugs singly. Opportunities to make a rational and comprehensive view of the DMTs may be lost or else have a disproportionate impact on those drugs which are appraised last. Current NICE guidance for some of the DMTs is predicated on prior treatment with one of several (but not all) of the current first line treatments. If additional drugs are approved for use in the NHS as first line treatments, this could create perverse constraints on access to 2nd or 3rd line treatments. This could potentially have a negative impact on patients for whom the most important issue is getting access to the right drug at the right time and not experiencing needless, avoidable and potentially burdensome delay. There is the prospect of increased choice but also increased complexity for patients and clinicians in weighing up the benefit and risk and making the best choice for each individual. It is crucial to do all that is possible to maximise clarity and minimise needless complexity. We would welcome consideration of the impact of any appraisals on all current NICE guidance. Clarification of the relationship between any or all of the drugs being appraised to the currently available DMTs would be welcome, including new and current sub-groups. Can NICE indicate how it proposes to manage the STA process for these new DMTs to avoid the introduction of additional constraints and ensure that those drugs licensed later are not disadvantaged? Can NICE indicate how it proposes to manage the increasing complexity of the prescribing landscape for DMTs?	Comments noted. The recommendations made by NICE in these single technology appraisals will be based on the assessment of the clinical and cost effectiveness of the technologies within their licensed indications for treating multiple sclerosis.

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		People who are stable on an injectable DMT should not be excluded from switching to an oral treatment if, following discussions with their neurologist, this is considered appropriate. The requirement for long-term injections places a burden on patients and can lead to reduced adherence. Self-injecting DMTs is painful, causes anxiety and stress; can lead to skin reactions and complications at injection sites; may be difficult for people whose manual dexterity is limited, requiring help from carers and families; imposes restrictions on travel. With respect to treatment sequencing, we wish to stress that there is no treatment pathway in place for disease modifying treatments and it is not within the scope of the current appraisal to be making assumptions on sequence or escalation of treatments. In UK clinical practice, switching or escalating treatments results from an individual's intolerable side effects or sub-optimal response to an initial treatment. An economic model cannot capture the benefit to the **individual** achieved by switching to an effective treatment. This reflects an urgent need within the UK for a much broader range of treatment options. As it is impossible to prognosticate for an individual, there is a need for flexibility to allow both clinician and patient to select a treatment that is both tolerable and effective for that person.	
	Novartis	No comments	Comment noted. No action required.
	Royal College of Nursing	To ensure people living with MS are informed that treatment intervention choice may remain limited despite spectrum of therapies becoming available.	Comment noted.
	Teva UK	The access to the data from the NHS risk-sharing scheme is limited, and the analytical methods are the subjects of significant and ongoing scientific and technical debate as the model is reviewed and updated. We would like to propose excluding this statement from the scope document until the data access and scientific and technical considerations have been resolved to the satisfaction of all parties. Additionally, Teva would welcome any support from the committee in facilitating data sharing from RSS and availability of the “no treatment” data (British Columbia natural history cohort dataset) from the	Comments noted. The arrangements within the risk-sharing scheme are based on agreement between the manufacturers and the Department of Health (and not NICE).

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		scheme.	The recommendations in NICE guidance are made by an independent Appraisal Committee. The manufacturer will be expected to provide clear reasoning within its evidence submission for the approaches taken to assess and validate the clinical and cost effectiveness of the technology of interest.
	United Kingdom Clinical Pharmacy Association	None	Comment noted. No action required.
Questions for consultation	Association of British Neurologists	N/A	Comment noted. No action required.
	MS Society	1) Would any people with relapsing-remitting MS be treated with 'best supportive care'? If so how should best supportive care be defined? Best supportive care with no disease modifying treatment is not a treatment option for relapsing forms of MS. Best supportive care is only a valid option where a patient has clear Secondary Progressive MS or Primary Progressive MS, without relapses. Laquinimod is unlikely to be indicated for either. The MS Society welcomes its exclusion from the list of comparators. There is no clinical definition of what constitutes best supportive care. It is not routinely used in clinical practice for the treatment of relapsing forms of MS therefore the MS Society fundamentally disagrees with the use of best supportive care as a comparator for DMTs for the treatment of relapsing-remitting MS. We strongly recommend that NICE do not use this as a	Comments noted. No action required.

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		comparator for any treatments indicated for relapsing forms of MS. The only circumstance that the MS Society would support the use of best supportive care would be as part of a blended-comparator. A blended comparator would consist of a combination of the proportion of those on available disease modifying treatments and an accurate proportion of those also receiving best supportive care - this would represent approximately 5 per cent of the population, as per research carried out by Dr Eli Silber. This would be a better reflection of the reality of the management of MS, which in clinical practice is a combination of both DMTs and care. A consensus statement by the MS Society, MS Trust and UKMSSNA on our view on best supportive care is attached in Appendix A.	
	MS Trust	The populations likely to be treated with laquinimod include treatment naïve, those who have not responded to prior DMTs, and those with intolerable side effects to DMTs. The MS Trust does not anticipate that laquinimod will be routinely used in highly active or rapidly evolving severe subgroups of MS. People who are stable on an injectable DMT should not be excluded from switching to an oral treatment if, following discussions with their neurologist, this is considered appropriate. The requirement for long-term injections places a burden on patients and can lead to reduced adherence. Self-injecting DMTs is painful, causes anxiety and stress; can lead to skin reactions and complications at injection sites; may be difficult for people whose manual dexterity is limited, requiring help from carers and families; imposes restrictions on travel. The draft scope raises the question of best supportive care. This reflects the fact that there is no clinical definition of "best supportive care" for people with RRMS; most clinicians would assert that best supportive care for eligible patients is actually first line treatment with a DMT. Standard care with no DMT is the least desirable and least common option for managing relapsing-remitting MS (RRMS), reserved largely for when all disease modifying therapies are poorly tolerated or the person with MS has	Comments noted. The recommendations made by NICE will be based on the assessment of the clinical and cost effectiveness of the technology within its licensed indication for treating multiple sclerosis. Consistent with other recent NICE single technology appraisals of treatments for relapsing-remitting multiple sclerosis, subgroups of patients will be considered if the evidence allows. See the 'other considerations' section of the scope.

Section	Consultees	Comments	Action
		expressed a strong and enduring preference for no treatment. Research evidence supports the treatment of people with RRMS early in the disease to prevent axonal damage and irreversible disability. Current practice in the management of RRMS is active and acknowledges that even if people with MS continue to have relapses while on therapy, they may still be deriving benefit from the treatment. People with MS often have limited access to services if they are not on a DMT; those on DMTs are more likely to be seen at regular intervals by an MS neurologist and MS specialist nurse and any symptoms actively managed, resulting in reduced unplanned hospital admissions. The use of DMTs is being justified at an increasingly early stage and in pre-MS syndromes such as clinically isolated and radiologically isolated syndromes. A consensus statement representing the views of the MS Trust, MS Society and UKMSSNA on the use of best supportive care as a comparator is attached in Appendix A.	
	Novartis	No comments	Comment noted. No action required.
	United Kingdom Clinical Pharmacy Association	none	Comment noted. No action required.
Additional comments on the draft scope.	Royal College of Nursing	Consideration must be given for Black Minority Ethnic (BME) groups within whom there is a significant cohort of People with MS. Consideration of the process of shared decision making as the complexity of treatment options increase. Consideration of the nature of comparators; the unique variability and unpredictability of clinical presentation and course of the disease requires a bespoke approach that need not necessarily follow a linear trajectory.	Comments noted. Considerations on uptake of the guidance is not part of the Appraisal Committee's remit. The comparators have been updated.
	United Kingdom Clinical Pharmacy	No further comments	Comment noted. No action required.

Section	Consultees	Comments	Action
	Association		

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

- Healthcare Improvement Scotland