National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Ocrelizumab for treating relapsing multiple sclerosis

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

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

Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Appropriateness	Biogen Idec	Yes.	Comment noted. No action required.
	Multiple Sclerosis Society	Yes, ocrelizumab has shown promising results for treating relapsing remitting MS (RRMS) in clinical trials reducing the number of relapses by 46% in OPERA I and 47% in OPERA II compared to Rebif. It also was shown to reduce disability progression by 43% in OPERA I and 37% in OPERA II, compared to Rebif. However, ocrelizumab has yet to be granted a marketing authorisation by the EMA so the appraisal timeline needs to fit with the EMA's licensing schedule.	Comments noted. No action required.
	Multiple Sclerosis Trust	Yes, we understand that the EMA CHMP is currently evaluating a marketing authorisation application for ocrelizumab for relapsing remitting MS.	Comment noted. No action required.
	Novartis Pharmaceuticals UK Ltd	No comments	Comment noted. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
	Roche Products Ltd	We believe it is appropriate to refer this topic to NICE for appraisal due to the complexity of the MS treatment landscape.	Comment noted. No action required.
	UK Clinical Pharmacy Association	Yes	Comment noted. No action required.
Wording	Biogen Idec	Yes.	Comment noted. No action required.
	Multiple Sclerosis Society	Yes	Comment noted. No action required.
	Multiple Sclerosis Trust	Yes, the draft remit reflects the issues that NICE should consider.	Comment noted. No action required.
	Novartis Pharmaceuticals UK Ltd	No comments	Comment noted. No action required.
	Roche Products Ltd	[redacted]	Comment noted. The remit states that the technology will be appraised within its marketing authorisation. No action required.
	UK Clinical Pharmacy Association	Yes	Comment noted. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
Timing Issues	Biogen Idec	N/A.	Comment noted. No action required.
	Multiple Sclerosis Society	We welcome NICE's timely consideration of ocrelizumab and urge them to conduct the appraisal as soon as possible in light of the EMA's decision on whether to grant daclizumab marketing authorisation.	Comment noted. NICE has scheduled this topic into its work programme. For further details, see the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ta10152. No action required.
	Multiple Sclerosis Trust	We would like to see NICE appraisal completed as soon as possible after licensing to ensure clarity about eligibility and availability within NHS England.	Comment noted. NICE has scheduled this topic into its work programme. For further details, see the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ta10152. No action required.
	Novartis Pharmaceuticals UK Ltd	No comments	Comment noted. No action required.

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	Roche Products Ltd	Several treatment options for relapsing forms of MS / RRMS have been appraised by NICE in recent years, and several new appraisals are ongoing or planned for upcoming years. Urgency is required to address the needs of patients with MS. There is increasing recognition within the MS expert community that disease activity in RRMS patients should be minimised across clinical and radiological / MRI parameters (1). The Association of British Neurologists (ABN) has recognised that currently available DMTs in the UK are effective in reducing relapses to varying degrees. The majority of available DMTs have been recognised to have moderate efficacy, whilst only two provide high efficacy (2). This includes agents with safety monitoring burden and potential short term treatment duration in patients with relevant risk factors (i.e. JCV status). The ABN guideline recognises the need for a range of DMTs to best meet the clinical needs of individual patients. **References:** (1) Giovannoni G, Butzkueven H, Dhib-Jalbut S, Hobart J, Kobelt G, Pepper G, et al. Brain health - Time matters in multiple sclerosis. 2016. (2) Scolding N, Barnes D, Cader S, Chataway J, Chaudhuri A, Coles A, et al. Association of British Neurologists: revised (2015) guidelines for prescribing disease-modifying treatments in multiple sclerosis. Pract Neurol 2015 Aug;15(4):273-9.	Comments noted. NICE has scheduled this topic into its work programme. For further details, see the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ta10152. No action required.
Any additional comments on the draft remit	Biogen Idec	N/A.	Comment noted. No action required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Biogen Idec	The Risk-Sharing Scheme (RSS) reached completion in March 2016. The Scheme as a whole can be considered a success and has received significant support throughout. The Scheme (and as a result of manufacturer contributions) has created the infrastructure to support the monitoring cohort and also to offer delivery of improved MS services for all people with MS across the country, not just services related with the prescription of DMTs. Beta interferon and glatiramer acetate are currently being assessing in a Multiple Technology Appraisal (MTA) TA32 by the National Institute for Heath and Care Excellence (NICE). A FAD is expected to be published in December 2016. Daclizumab is currently undergoing a Single Technology Appraisal (STA) by NICE, with a FAD expected January 2017. Spelling error in third paragraph: the correct spelling is “dimethyl fumarate”	Comments noted. The spelling error has been corrected and the daclizumab appraisal (TA441) has been added to the background section and list of related technology appraisals.
	Multiple Sclerosis Society	The background covers the population and treatments currently available for RRMS. However, the importance of early treatment for MS should be emphasised as the recognised medical consensus is that the earlier treatment is administered the better the outcomes will be for the person diagnosed. This should be reflected in the background information as it is important that people with MS should be able to choose their first line of treatment when consulting with a neurologist. Please see the following links for more information: MS Society website for further details http://www.mssociety.org.uk/earlytreatment The Association of British Neurologist’s most recent guidelines http://pn.bmj.com/content/early/2015/06/20/practneurol-2015-001139.full	Comments noted. This section of the scope aims to provide a brief overview of the background for the appraisal; additional details may be considered by the committee, if appropriate, at the time of the appraisal. No action required.

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		The MS Brain Health initiative http://www.msbrainhealth.org/	
	Multiple Sclerosis 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.	Comments noted. This section of the scope aims to provide a brief overview of the background for the appraisal; additional details may be considered by the committee, if appropriate, at the time of the appraisal. No action required.
	Novartis Pharmaceuticals UK Ltd	No comments	Comment noted. No action required.
	Roche Products Ltd	No comment	Comment noted. No action required.
	Teva UK Ltd	The questions are reasonable and the data appear accurate. For the detailed questions, it's difficult to offer input without sight of the file. As a monoclonal antibody, cost and safety will be paramount If the SmPC was available (which it is not), this could serve as the basis for providing further responses to the various questions on the draft scope	Comments noted. No action required.

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	UK Clinical Pharmacy Association	Yes	Comment noted. No action required.
The technology/ intervention	Biogen Idec	Yes.	Comment noted. No action required.
	Multiple Sclerosis Society	The brand name is Ocrevus. Frequency of administration should also be included as this plays a significant role in adherence rates of treatments.	Comments noted. The brand name has been added to the scope. This section of the scope aims to provide a brief overview of the technology for the appraisal; additional details may be considered by the committee, if appropriate, at the time of the appraisal.
	Multiple Sclerosis Trust	Brand name now published - Ocrevus.	Comment noted. The brand name has been added to the scope.
	Novartis Pharmaceuticals UK Ltd	No comments	Comment noted. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
	Roche Products Ltd	The brand name of ocrelizumab is Ocrevus.	Comment noted. The brand name has been added to the scope.
	UK Clinical Pharmacy Association	Yes	Comment noted. No action required.
Population	Biogen Idec	People with relapsing forms of multiple sclerosis (RMS) include: • People with RRMS (relapsing remitting MS) and • People with relapsing SPMS (secondary progressive MS). For comparators, clinical trials were mainly conducted in RRMS patients. Therefore, we believe that people with RRMS and people with relapsing SPMS should be considered separately, in addition to the RMS group. The questions for consultation include the potential use of the technology in the CIS (clinically isolated syndrome) population. We are not aware of clinical trial data in CIS for the technology. Any analysis in the CIS population would depend on the technology's licensed indication.	Comments noted. The scope has been amended to include the following subgroups of people with: • relapsing-remitting multiple sclerosis • rapidly-evolving severe relapsing-remitting multiple sclerosis • highly active relapsing-remitting multiple sclerosis despite previous treatment • secondary progressive multiple sclerosis with active disease, evidenced by relapses.

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	Multiple Sclerosis Society	Yes	Comment noted. No action required.
	Multiple Sclerosis Trust	Depending on marketing authorisation, the populations likely to be treated with ocrelizumab include treatment naïve, those who have not responded to prior disease modifying drugs (DMDs), and those with intolerable side effects to DMDs. 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 available data does not include in-depth analysis of these sub-groups.	Comments noted. NICE appraises technologies within their marketing authorisation. Several comparators are recommended only for the specific subgroups of highly active or rapidly evolving severe relapsing-remitting multiple sclerosis, and these distinctions are made in the scope for clarity. No action required.
	Novartis Pharmaceuticals UK Ltd	Under the “Population” section, the final scope for daclizumab used the term “adults”, rather than the term “people” that is used in the ocrelizumab draft scope. Please can NICE confirm that “people” refers to adults over the age of 18 years of age? If this is the case, we would suggest that it would be preferential to use “adults” in the ocrelizumab draft scope in order to make it unambiguous as to what population is being considered and remove any doubt about consideration of paediatric patients within this appraisal. If the questions for consultation conclude that the scope will also cover “secondary progressive multiple sclerosis with active disease, evidenced by relapses” or “clinically isolated syndrome” then it would be helpful to clarify	Comments noted. The scope has been kept broad to ensure that NICE can appraise the technology within its marketing authorisation. The scope has been amended to include the following subgroups of people with:

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		that these populations will be analysed separately, as the comparators, costs and health effects are likely to be different from those in RRMS.	• relapsing-remitting multiple sclerosis • rapidly-evolving severe relapsing-remitting multiple sclerosis • highly active relapsing-remitting multiple sclerosis despite previous treatment • secondary progressive multiple sclerosis with active disease, evidenced by relapses.
	Roche Products Ltd	[redacted]	Comment noted. The remit states that the technology will be appraised within its marketing authorisation. No action required.
	UK Clinical Pharmacy Association	Consider evidence or lack thereof for ocrelizumab in secondary progressive MS using beta interferon as a comparator.	Comment noted. In other similar appraisal topics in this disease area, clinical experts have highlighted that beta interferons are

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			rarely used in clinical practice and therefore has not been included in the list of comparators. No action required.
Comparators	Biogen Idec	We are not aware of any established treatment for RMS. The comparator treatments listed are all used in RRMS. We are not aware of any treatments for relapsing SPMS currently established in UK clinical practice. Regarding CIS, although most interferons are licensed in this indication, we believe that treatment is not routinely initiated at the time of diagnosis of CIS.	Comments noted. For clarity, the scope has been amended to include comparators (as recommended by NICE, where relevant) specific to the following subgroups of people with: • relapsing-remitting multiple sclerosis • rapidly-evolving severe relapsing-remitting multiple sclerosis • highly active relapsing-remitting multiple sclerosis despite previous treatment • secondary progressive multiple sclerosis with active

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			disease, evidenced by relapses.
	Multiple Sclerosis Society	No single comparator would be seen as a 'best alternative care', treatment options depend upon personal preference, severity of MS, side effects and efficacy experienced. The comparators listed in the draft scope risk being overly prescriptive and rigid, which does not represent the reality in clinical practice. They also do not include all treatments which could fit within each category, see below: • **People who have not had treatment previously** The DMTs listed here are accurate to their licenses only when not including people with highly active MS. • **People who have had previous treatment** This category is confusing as all treatments could seemingly fit within it? People tend to switch between treatments due to side effects or because they are not responding well to their current treatment. In the latter case they are likely to switch to one of the following more efficacious treatments: alemtuzumab, dimethyl fumurate, natalizumab or fingolimod. They are unlikely to switch to teriflunomide which is a less effective option. If people are switching due to side effects, they may well switch to another treatment of similar efficacy. • **People with rapidly-evolving severe relapsing remitting MS** This category should also include fingolimod. • **People with highly active RRMS despite previous treatment** This category should also include natalizumab.	Comments noted. NICE appraises technologies within their marketing authorisation. For clarity, the scope has been amended to include comparators (as recommended by NICE, where relevant) specific to the following subgroups of people with: • relapsing-remitting multiple sclerosis • rapidly-evolving severe relapsing-remitting multiple sclerosis • highly active relapsing-remitting multiple sclerosis despite previous treatment • secondary progressive multiple sclerosis with active

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		In practice, the terms 'highly active' and 'rapidly evolving severe' MS are interchangeable. The latter two categories should use the same terminology to describe aggressive forms of MS to avoid confusion.	disease, evidenced by relapses.
	Multiple Sclerosis Trust	Depending on marketing authorisation, all of the listed comparators should be included. No single comparator would be seen as a best alternative care, but treatment with any one of these DMTs would be viewed as standard treatment. Choice of DMD is made in partnership between prescribing neurologist and the person living with MS. Treatment selection is increasingly personalised, reflecting clinical and sub-clinical disease activity and any issues regarding drug tolerance as well as patient risk attitudes and their view about the balance of risk, benefit and commitment regarding treatment and monitoring. The subgroups of comparators listed have become increasingly complex and are not as mutually exclusive as these lists suggest. The use of the drugs within their licensed indications and NICE TAs overlaps to a much greater extent than these subgroups suggest. For example, there may be good reason for a 'lateral' switch to agents of broadly similar efficacy, perhaps due to tolerability or compatibility with personal circumstances. We would discourage viewing the comparators too rigidly, as the listed subgroups imply. We recognise that there are a growing number of disease modifying drug treatments and, as yet, no clear consensus about sequencing. Real world experience with the newer agents is still growing. If granted, the marketing authorisation for ocrelizumab will help to broadly place the drug in some relation to the other treatments.	Comments noted. NICE appraises technologies within their marketing authorisation. For clarity, the scope has been amended to include comparators (as recommended by NICE, where relevant) specific to the following subgroups of people with: • relapsing-remitting multiple sclerosis • rapidly-evolving severe relapsing-remitting multiple sclerosis • highly active relapsing-remitting multiple sclerosis despite previous treatment • secondary progressive multiple sclerosis with active

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			disease, evidenced by relapses.
	Novartis Pharmaceuticals UK Ltd	**1.Inappropriate population distinctions** The Comparators Section proposes a split between "people who have received previous treatment" and "people with highly active relapsing-remitting multiple sclerosis despite previous treatment". We believe that this is an unhelpful and inappropriate distinction as these groups are largely overlapping. The distinction may have stemmed from the definition of "highly active" disease. In the original label for fingolimod (a comparator in the draft scope), this had a very specific definition, as was also the case for the natalizumab label (another comparator). However, we would like to draw NICE's attention to the fact that a label change has recently occurred for fingolimod, where the indication has been simplified and clinicians are now able to decide what constitutes "highly active" disease using their clinical judgement ((https://www.medicines.org.uk/emc/medicine/24443 accessed 04/05/2016). The wording of the fingolimod label for highly active RRMS is now: "Gilenya is indicated as single disease modifying therapy in highly active relapsing remitting multiple sclerosis for ... patients with highly active disease despite a full and adequate course of treatment with at least one disease modifying therapy". It is anticipated that a DMT switch due to new or worsening symptoms whilst on therapy is likely to constitute "highly active disease". Therefore the distinction in the ocrelizumab draft scope between people who "have not had treatment previously" and people "who have had previous treatment" is rendered largely redundant. We believe the distinction between "people who have received previous treatment" and "people with highly active relapsing-remitting multiple sclerosis	Comments noted. For clarity, the scope has been amended to include comparators (as recommended by NICE, where relevant) specific to the following subgroups of people with: • relapsing-remitting multiple sclerosis • rapidly-evolving severe relapsing-remitting multiple sclerosis • highly active relapsing-remitting multiple sclerosis despite previous treatment • secondary progressive multiple sclerosis with active disease, evidenced by relapses.

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		despite previous treatment" in the draft scope has come about from comments made by the MS Trust during the scoping consultation for daclizumab. These comments were made on the "Other considerations" section of the scope rather than the "Comparators" section (Scoping consultation comments summary p13-14). As outlined in our correspondence regarding the daclizumab final scope, we believe this may be an incorrect interpretation of the MS Trust's comment since they also argue, in the next paragraph of their response, against over-specification of treatment sequencing. **2. Matching terminology of the scope with DMT marketing authorisation terminology** "Had previous treatment" is not a subgroup that has been used by the European Medicines Agency (EMA) to define indications, whereas "highly active relapsing-remitting multiple sclerosis despite previous treatment" has been used by the EMA. Therefore we would suggest that the "had previous treatment" category is removed from the scope. Such an arrangement of the scope removes the requirements for further novel data cuts, the analyses for which are likely to be underpowered and not to have been based on the stratification factors at randomisation in the pivotal trials, thereby potentially introducing bias to these analyses. If left in, it will exacerbate an already complex set of post-hoc analyses. To summarise, the categorization of "had previous treatment" is likely to cause confusion and may not offer any pragmatic benefit for decision-making. Novartis recommends that the draft scope should be revised by removing the "had previous treatment" group and renaming the "not had treatment previously" group as an "active disease" group. The terminology of "active disease" has previously been used by the European Medicines Agency (EMA) to define indications. This "active disease" group can then include the comparators that would be considered if people switch first-line therapy due to adverse events or tolerability or due to efficacy reasons.	

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		3.Inclusion of Fingolimod as a comparator for rapidly evolving severe (RES) disease The NHS England Commissioning Policy "Disease Modifying Therapies for Patients with Multiple Sclerosis (MS)" (May 2014, Reference: NHS ENGLAND/D04/P/b) recommends the use of fingolimod as an option in RES patients who are on natalizumab and at high risk of developing PML. If the Scope is to reflect "established NHS practice in England", it should be amended to include fingolimod as a comparator alongside natalizumab and alemtuzumab in the RES RRMS subgroup. (Guide to the methods of technology appraisal, 2013, 6.2.2 p66). **Revised comparators proposal:** Novartis therefore proposes that the final scope for comparators should read as follows: For people with active RRMS • alemtuzumab • dimethyl fumarate • teriflunomide • beta-interferon • glatiramer acetate For people with highly active relapsing-remitting multiple sclerosis despite previous treatment • alemtuzumab • fingolimod For people with rapidly-evolving severe relapsing-remitting multiple sclerosis • alemtuzumab	

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		• natalizumab • fingolimod	
	Roche Products Ltd	We believe that treatments should not be split by treatment-naïve or treatment-experienced, unless directed by the wording of the marketing authorisation and/or NICE recommendation. We are only aware of this being the case for natalizumab in rapidly evolving severe (RES) disease and fingolimod in highly active (HA) disease despite previous treatment. The marketing authorisations and NICE recommendations for beta-interferons and glatiramer acetate are not restricted to treatment-naïve patients only. Although generally used in the first-line setting, these treatment options can also be given in later lines for reasons of tolerability. Furthermore, pivotal studies of most medicines in MS (including ocrelizumab) contain mixed patient populations and it would add uncertainty if additional post hoc analyses were needed to synthesise evidence in a network meta-analysis. The NICE Guide to Methods (section 5.10.6) also states that lack of pre-specification of subgroups in studies decreases the credibility of subgroup analyses (3). **References:** (3) NICE. Guide to the methods of technology appraisal. 2013.	Comments noted. For clarity, the scope has been amended to include comparators (as recommended by NICE, where relevant) specific to the following subgroups of people with: • relapsing-remitting multiple sclerosis • rapidly-evolving severe relapsing-remitting multiple sclerosis • highly active relapsing-remitting multiple sclerosis despite previous treatment • secondary progressive multiple sclerosis with active disease, evidenced by relapses.

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	Teva UK Ltd	For glatiramer acetate, it is assumed that this refers to Copaxone 20mg & 40mg combined. However, if ocrelizumab is intended for second-line indication, Copaxone may not be the most relevant comparator	Comments noted. For clarity, the scope has been amended to include comparators (as recommended by NICE, where relevant) specific to the following subgroups of people with: • relapsing-remitting multiple sclerosis • rapidly-evolving severe relapsing-remitting multiple sclerosis • highly active relapsing-remitting multiple sclerosis despite previous treatment • secondary progressive multiple sclerosis with active disease, evidenced by relapses.

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Outcomes	Biogen Idec	Yes.	Comment noted. No action required.
	Multiple Sclerosis Society	In considering freedom from disease activity, which is welcome, value should also be given to steps towards that goal in terms of suppression of disease activity. To gain a fuller understanding of disease activity a full range of indicators should be 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)	Comments noted. **This section of the scope aims to provide a brief overview of the important outcomes for the appraisal.** The most appropriate definition of 'freedom from disease activity' will be explored during the appraisal, but may include subclinical indicators. The list of symptoms in the scope is not intended to be exhaustive, but includes cognition and fatigue. No action required.
	Multiple Sclerosis Trust	Relapses have a significant impact on daily life eg work, family commitments, leisure activities. This aspect of relapse control has great relevance to patients, as well as clinical measures. The outcome measures should reflect the wider social and economic impact of MS relapses such as days of work lost, change in employment status. Patient reported outcome measures PROMS should be included.	Comments noted. In line with NICE reference case, costs are considered from the NHS and Personal Social Services perspective, which does

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		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. Instrument selection for outcome measurement of symptoms such as fatigue and cognition in MS are still an evolving area. Multiple instruments are currently in use across clinical trials in MS and it will be important to critically consider instrument selection as well as the results they demonstrate in the data submitted. Freedom from disease activity is also an evolving concept in MS and there is not yet a fully settled definition of the term, particularly with respect to the critical measures of sub-clinical disease activity. Some definitions include measurement of total brain volume (TBV) in addition to presence of brain lesions on MRI scans. To be useful in the clinical setting, the exact detail of the outcome measure needs further clarification and definition to guide prescribing and to help people living with MS understand the goals of treatment and help them in making their treatment choices. This may be best facilitated by separating out the measures aggregated in the concept of freedom from disease activity. For instance, number of lesions on MRI scans, as the prime sub-clinical measure may be best treated as a separate measure. The MS Trust supports greater attention to clinical and sub-clinical measures of disease activity in RRMS to inform treatment strategies and a more proactive approach to initiating treatment with a DMD early and an escalation strategy if evidence of disease activity is present on current treatment.	not include caregiver burden or lost work productivity. The committee, at its discretion, may request non-reference case analyses if appropriate. This section of the scope aims to provide a brief overview of the important outcomes for the appraisal. The list of symptoms of multiple sclerosis or specific outcome measures are not intended to be exhaustive. Patient reported outcome measures will be captured within the outcomes in the scope. The most appropriate definition of 'freedom from disease activity' will be explored during the appraisal, but may include subclinical indicators. No action required.

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	Novartis Pharmaceuticals UK Ltd	No comments	Comment noted. No action required.
	Roche Products Ltd	Yes we believe the outcome measures listed are relevant for RRMS, but we do have a few comments. The more recognised term for freedom from disease activity is “no evidence of disease activity” (i.e. NEDA), which typically incorporates relapse, disability and MRI measures (specifically T2 and gadolinium enhancing lesions). We believe that consideration of individual MRI components is warranted as neurologists consider these to be more sensitive in detecting underlying inflammatory activity than overt clinical relapses (2). Brain volume is a measure of diffuse brain damage. Loss of brain volume is recognised as an important emerging clinical measure which correlates with disability progression and cognitive impairment, and has been noted in early MS (4). However this measure is not yet routinely used in clinical practice. **References:** (2) Scolding N, Barnes D, Cader S, Chataway J, Chaudhuri A, Coles A, et al. Association of British Neurologists: revised (2015) guidelines for prescribing disease-modifying treatments in multiple sclerosis. Pract Neurol 2015 Aug;15(4):273-9. (4) De Stefano N., Airas L, Grigoriadis N, Mattle HP, O'Riordan J, Oreja-Guevara C, et al. Clinical relevance of brain volume measures in multiple sclerosis. CNS Drugs 2014 Feb;28(2):147-56.	Comments noted. This section of the scope aims to provide a brief overview of the important outcomes for the appraisal. The most appropriate definition of ‘freedom from disease activity’ will be explored during the appraisal, but may include subclinical indicators. No action required.
	UK Clinical Pharmacy Association	Yes	Comment noted. No action required.

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Economic analysis	Biogen Idec	N/A.	Comment noted. No action required.
	Multiple Sclerosis 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 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 (MS Society, 2010). It must be taken into account that MS is frequently 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 71% of people with MS receive support or assistance from friends and family members (MS Society, A lottery of treatment and care: MS services across the UK, April 2013). 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 report found that the "professional careers of 57 per cent of relatives are adversely affected by MS of a family member 2011: 4)	Comments noted. In line with NICE reference case, costs are considered from the NHS and Personal Social Services perspective, which does not include caregiver burden or lost work productivity. The committee, at its discretion, may request non-reference case analyses if appropriate. No action required.

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		- the value of informal care (unpaid care in the UK has been estimated at £132bn, almost exactly the value of health spending in the UK, £134bn. Carers UK State of Caring 2016) - 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, 2012, Carers Week). - increased tax revenue (Kennedy, 2009: 27)	
	Multiple Sclerosis 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. In line with NICE reference case, costs are considered from the NHS and Personal Social Services perspective, which does not include caregiver burden or lost work productivity. The committee, at its discretion, may request non-reference case analyses if appropriate. No action required.
	Novartis Pharmaceuticals UK Ltd	No comments	Comment noted. No action required.

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	Roche Products Ltd	Social care plays an important role in the wellbeing of patients with MS. Nearly one-third of people with MS need care; the great majority of which is provided 'informally' by unpaid caregivers such as relatives (1). Therefore the burden of disability progression falls not just on people with MS but also on their families. Caregivers' health-related quality of life deteriorates as the person with the disease becomes more disabled. We believe it would therefore be important to capture this in the economic analysis of ocrelizumab in RRMS. **Reference:** (1) Giovannoni G, Butzkueven H, Dhib-Jalbut S, Hobart J, Kobelt G, Pepper G, et al. Brain health - Time matters in multiple sclerosis. 2016.	Comments noted. In line with NICE reference case, costs are considered from the NHS and Personal Social Services perspective, which does not include caregiver burden. The committee, at its discretion, may request non-reference case analyses if appropriate. No action required.
Equality and Diversity	Biogen Idec	N/A.	Comment noted. No action required.
	Multiple Sclerosis Trust	No equality issues to highlight.	Comment noted. No action required.
	Novartis Pharmaceuticals UK Ltd	No comments	Comment noted. No action required.
	Roche Products Ltd	We do not believe the proposed remit and scope need changing to meet the aim of equality.	Comment noted. No action required.
	UK Clinical Pharmacy Association	No	Comment noted. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
Other considerations	Biogen Idec	By dividing the patient population with RMS into the requested populations, fewer comparisons will be possible between treatments. There will be a lack of data for comparators in RMS to form indirect comparisons.	Comments noted. The subgroups will be considered only if the evidence allows. If there is insufficient evidence to allow robust analyses, the company can make a case for deviating from the scope and/or present sensitivity analyses around its base case. No action required.
	Multiple Sclerosis Society	The latter subgroup 'people with relapsing-remitting multiple sclerosis who could not tolerate previous treatment', needs to clarify what it counts as 'could not tolerate'. Intolerable side effects are subjective, for some the effects of some of the first line injectables may be intolerable but not considered seriously adverse.	Comments noted. For clarity, the scope has been amended to include the following subgroups of people with: • relapsing-remitting multiple sclerosis • rapidly-evolving severe relapsing-remitting multiple sclerosis • highly active relapsing-remitting multiple sclerosis

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			despite previous treatment • secondary progressive multiple sclerosis with active disease, evidenced by relapses.
	Novartis Pharmaceuticals UK Ltd	No comments	Comment noted. No action required.
	Roche Products Ltd	We do not believe that evidence allows for consideration of subgroups of patients who switched treatment due to efficacy versus tolerability reasons (see comments in Comparators section above). Ocrelizumab is also expected to be used in patients with RES RRMS, and in HA RRMS despite previous treatment. Subgroup analyses will be available for these sub-populations at the time of NICE submission.	Comments noted. For clarity, the scope has been amended to include the following subgroups of people with: • relapsing-remitting multiple sclerosis • rapidly-evolving severe relapsing-remitting multiple sclerosis • highly active relapsing-remitting multiple sclerosis despite previous treatment

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			• secondary progressive multiple sclerosis with active disease, evidenced by relapses.
Innovation	Biogen Idec	N/A.	Comment noted. No action required.
	Multiple Sclerosis Society	Yes, trials have shown ocrelizumab to be highly effective and generally well tolerated. Two phase 3 trials (OPERA I and OPERA II) were completed in June 2015 and Roche reported positive outcomes for the effectiveness of ocrelizumab as a treatment for relapsing remitting MS against interferon beta-1a (also known as Rebif). The trials involved over 1,600 people and after two years, the study is reported to show that ocrelizumab reduced the annual relapse rate by 46% in OPERA 1, 47% in OPERA II and the progression of clinical disability by 40%, as measured by the Expanded Disability Status Scale (EDSS). Additionally, the study has been reported to show that ocrelizumab reduced the number of lesions in the brain, as measured by MRI scans by 94%. Roche have also reported at a conference in April 2016 that around 50% of people taking ocrelizumab saw no evidence of disease activity (NEDA) in both OPERA I and OPERA II, this was compared to 25-30% of people taking interferon-beta-1a. NEDA is defined as no relapses, no confirmed disability progression as measured by EDSS, and no new or enlarging lesions.	Comments noted. The appraisal committee will discuss the potentially innovative nature of this technology. No action required.
	Multiple Sclerosis Trust	Yes, ocrelizumab has a novel mechanism of action, a novel treatment schedule and greater efficacy than some of the existing DMDs. From the available data, it appears to be well-tolerated. A drug which is both highly effective and very safe has the potential to be a welcome and valuable addition to the range of available treatments.	Comments noted. The appraisal committee will discuss the potentially innovative nature of this

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			technology. No action required.
	Novartis Pharmaceuticals UK Ltd	No comments	Comment noted. No action required.
	Roche Products Ltd	We consider ocrelizumab to be innovative as it targets a specific subpopulation of immunological cells recognised to have a central role in the pathophysiology of MS, namely CD20 expressing B lymphocytes, which contrasts to other therapeutic options in MS (5). Ocrelizumab also has the unique potential to combine high efficacy with a favourable safety profile and convenient dosing schedule, based on data from the two pivotal phase 3 studies. **Reference:** (5) Hauser SL. The Charcot Lecture | beating MS: a story of B cells, with twists and turns. Mult Scler 2015 Jan;21(1):8-21.	Comments noted. Innovation will be considered by the appraisal committee when formulating its recommendations. The company will have an opportunity to provide evidence on the innovative nature of its product in its submission. No action required.
	UK Clinical Pharmacy Association	Ocrelizumab has a different mechanism of action to existing MS disease modifying therapies. It offers a further treatment option for people with relapsing MS.	Comments noted. The appraisal committee will discuss the potentially innovative nature of this technology. No action required.
Questions for consultation	Biogen Idec	N/A.	Comment noted. No action required.

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	Multiple Sclerosis Society	Ocrelizumab is expected to treat all people with MS where relapses and/or inflammatory damage are a major feature. Clinically isolated syndrome should be considered separately due to the differing level of evidence around the number of people who develop MS and therefore the differing effectiveness of treatment. Also people with clinically isolated syndrome were not included in the clinical trials.	Comments noted. Clinically isolated syndrome has not been included in the scope. No action required.
	Multiple Sclerosis Trust	**Is ocrelizumab expected to be used to treat:** • **secondary progressive multiple sclerosis with active disease, evidenced by relapses?** Yes, people with secondary progressive MS with relapses were included in the OPERA I and OPERA II clinical trials, so this group could be treated. In clinical practice it is very difficult to distinguish between RRMS and SPMS with relapses. • **clinically isolated syndrome, that is, a single demyelinating event, who are considered at high risk of developing multiple sclerosis?** No, clinically isolated syndrome has not been investigated in ocrelizumab clinical trials so we would not expect this use at the present time. • **rapidly-evolving severe relapsing-remitting multiple sclerosis?** Yes, clinical trials have shown ocrelizumab to be very effective at reducing relapse rates and it is likely that it would be considered for this use by MS neurologists. • **highly active relapsing-remitting multiple sclerosis despite previous treatment?**	Comments noted. For clarity, the scope has been amended to include comparators (as recommended by NICE, where relevant) specific to the following subgroups of people with: • relapsing-remitting multiple sclerosis • rapidly-evolving severe relapsing-remitting multiple sclerosis • highly active relapsing-remitting multiple sclerosis despite previous treatment • secondary progressive multiple

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		Yes, clinical trials have shown ocrelizumab to be more effective than first line treatments (interferon beta 1a, Rebif) so we would expect it to be used to treat people who continue to have relapses despite treatment. **Have all relevant comparators for ocrelizumab been included in the scope?** Yes, all of the treatments currently approved for treating relapsing remitting MS are included in the scope. **Which treatments are considered to be established clinical practice in the NHS for:** • **relapsing-remitting multiple sclerosis?** No single treatment would be seen as established clinical practice, but treatment with any one of these DMTs would be viewed as standard treatment. • **secondary progressive multiple sclerosis with active disease, evidenced by relapses?** No single treatment would be seen as established clinical practice. • **clinically isolated syndrome, that is, a single demyelinating event, who are considered at high risk of developing multiple sclerosis?** No single treatment would be seen as established clinical practice. **Are the outcomes listed appropriate?** See our comments above. **Are the subgroups suggested in 'other considerations' appropriate?** See our comments above.	sclerosis with active disease, evidenced by relapses. Comments noted. See relevant sections for specific response. No action required.

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		Are there any other subgroups of people in whom ocrelizumab is expected to be more clinically effective and cost effective or other groups that should be examined separately? See our comments above. **Where do you consider ocrelizumab will fit into the existing NICE pathway for multiple sclerosis?** See our comments above in the section on comparators. Disease modifying treatment of multiple sclerosis is managed in partnership between the prescribing neurologist and the person living with MS. Many of the sub-groups defined by the regulator and then reflected on in previous technology appraisals do not match well with the realities of prescribing in the real world clinical setting. In this context prescribing neurologists, supported by MS specialist nurses are assessing disease activity and its impact on the person living with the condition. The person with MS must make their unique and vital contribution to treatment selection, being able to reflect their attitude to risk, their commitment to longterm administration and monitoring regimes and their personal goals regarding their life with MS.	
	Novartis Pharmaceuticals UK Ltd	No comments	Comment noted. No action required.
	Roche Products Ltd	The phase 3 studies evaluating ocrelizumab in RRMS were not specifically designed to explore the SPMS patient population. [redacted] Since the 2010 McDonald criteria, CIS can be classified as RRMS and is therefore no longer considered a separate sub-population. We do not believe there are any other subgroups of patients (apart from RES and HA despite previous treatment, see comments in Other considerations section above) in whom ocrelizumab is expected to be more clinically	Comments noted. For clarity, the scope has been amended to include the following subgroups of people with: • relapsing-remitting multiple sclerosis

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		effective and cost effective, or other groups that should be examined separately.	• rapidly-evolving severe relapsing-remitting multiple sclerosis • highly active relapsing-remitting multiple sclerosis despite previous treatment • secondary progressive multiple sclerosis with active disease, evidenced by relapses.
	Sanofi Genzyme	Under the question "Is ocrelizumab expected to be used to treat" we would suggest that you add primary progressive MS (p. 5) In answer to the question Where do you consider ocrelizumab will fit into the existing NICE pathway for multiple sclerosis? (p. 6) we would suggest the following: • Rapidly-evolving severe relapsing-remitting multiple sclerosis where treatment with alemtuzumab / natalizumab has failed or cannot be tolerated • For people with highly active relapsing-remitting multiple sclerosis despite previous treatment where treatment with alemtuzumab has failed or cannot be tolerated • Primary Progressive MS where benefit of treatment outweights potential risk	Comments noted. There is a separate appraisal for primary progressive multiple sclerosis (ID938). For clarity, the scope has been amended to include the following subgroups of people with: • relapsing-remitting multiple sclerosis • rapidly-evolving severe relapsing-

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		In answer to the question "Do you consider ocrelizumab to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?" (p.7) we would suggest the following answer: • Ocrelizumab could be considered innovative in PPMS. In RRMs ocrelizumab is not innovative as treatment is not finite and there is no additional clinical benefit over and above alemtuzumab, therefore leading to increased QALY costs for no additional clinical benefit In answer to the question "Do you consider that the use of ocrelizumab can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?" (p.7) we would suggest the answer is no.	remitting multiple sclerosis • highly active relapsing-remitting multiple sclerosis despite previous treatment • secondary progressive multiple sclerosis with active disease, evidenced by relapses. The appraisal committee will discuss the potentially innovative nature of this technology.
	UK Clinical Pharmacy Association	We consider that ocreluzumab should fit into the disease modifying therapies section of the existing NICE pathway for MS	Comment noted. No action required.
Additional comments on the draft scope	Biogen Idec	N/A.	Comment noted. No action required.
	Multiple Sclerosis Society	The current daclizumab appraisal is missing from the 'Appraisals in development' section.	Comment noted. The daclizumab appraisal (TA441) has been added to the background section and

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			list of related technology appraisals.
	Multiple Sclerosis Trust	Related national policy should include the revised (2015) prescribing guidelines for disease modifying therapy from the Association of British Neurologists - we would highlight a change in the treatment paradigm for RRMS, emphasising the importance of early treatment. This is reflected in the revised ABN guideline and has implications for the eligibility criteria for starting disease modifying treatment that currently apply. Scolding N, Barnes D, Cader S, Chataway J, Chaudhuri A, Coles A, et al. Association of British Neurologists: revised (2015) guidelines for prescribing disease-modifying treatments in multiple sclerosis. Practical Neurology. 2015 Aug 1;15(4):273–9.	Comments noted. The related national policy usually refers only to NHS England and Department of Health policies. No action required.

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

Department of Health
Merck Serono