NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Ocrelizumab for treating relapsing multiple sclerosis [ID937]

The following documents are made available to the consultees and commentators:

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

2. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   - Roche Products Ltd
   - Multiple Sclerosis Society
   - Multiple Sclerosis Trust
   - Association of British Neurologists
   - Sanofi Genzyme
   - Novartis

   DHSC submitted a "no comments" response

3. **Comments on the Appraisal Consultation Document from experts:**
   - Dr Helen Ford, clinical expert, nominated by Novartis Pharmaceuticals UK Ltd
   - Dr David Hunt, clinical expert, nominated by the Multiple Sclerosis Society

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

5. **Additional evidence provided by the company, Roche Products Ltd**

6. **Evidence Review Group review of additional evidence prepared by** Southampton Health Technology Assessments Centre

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

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Ocrelizumab for treating relapsing multiple sclerosis

Single/Multiple Technology Appraisal

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

Type of stakeholder:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and Social Care and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal document (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation.

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health and Social Care, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

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

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
1	Consultee	Roche Products Ltd; hereinafter "Roche"	Roche appreciates the opportunity to provide comments on the NICE Appraisal Consultation Document (ACD) for 'Ocrelizumab for treating relapsing multiple sclerosis [ID937]'. While disappointed that the Committee was unable to recommend ocrelizumab in the ACD, Roche is committed to clarifying the remaining uncertainties to ensure ocrelizumab becomes available to NHS patients. Roche have also submitted a revised Patient Access Scheme for ocrelizumab to support committee decision making in determining ocrelizumab to be a cost-effective treatment option within its marketing authorisation. Roche have submitted an appendix with a revised base case in line with the committee's preferred assumptions: • used mixed treatment comparison estimates for confirmed disability progression at 6 months, with missing data imputed based on 3-month data (see details below and in the Roche ACD response Appendix) • included the potential risk of progressive multifocal leukoencephalopathy (PML) for ocrelizumab (using data from rituximab in rheumatoid arthritis as proxy, see details below) • provided cost-effectiveness estimates for each beta interferon and glatiramer acetate compared with ocrelizumab • used UK MS Survey as the source of EDSS costs • used treatment stopping rates for ocrelizumab and all comparators from the mixed treatment comparison in the absence of evidence for a treatment waning effect (same as in previous base case) However, Roche believe that several conclusions in the ACD are not a reasonable and equitable interpretation of the evidence and encourage the Committee to reconsider its conclusions. The responses below address these themes in turn: • disability progression • subgroups • safety profile • innovation • individual comparisons to beta-interferons and glatiramer acetate • waning of treatment effect	Thank you for your comment. The committee considered the revised base case and the FAD has been amended to reflect this – see FAD sections 3.5, 3.10, 3.11, 3.15. and 3.18.
2	Consultee	Roche	**Disability progression**	Thank you for your comment. The committee

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			The ACD states in 3.9 that *'the committee concluded that it was uncertain whether ocrelizumab slowed disability progression in the whole relapsing–remitting multiple sclerosis population compared with other treatments because there were differences in the effect size between confirmed disability progression at 3 months and 6 months.'* It also states in 3.11 that *'It would be appropriate to use a mixed treatment network to jointly model the outcomes for continued disease progression at 3 months and 6 months.'* Evidence from the OPERA trials confirms that ocrelizumab is a superior treatment to IFNB-1a (Rebif), with high and consistent efficacy in delaying confirmed disability progression (CDP). The direct evidence is clear: ▪ ocrelizumab is the only disease modifying therapy (DMT) that consistently demonstrated statistically significant reduction in confirmed disability progression as expressed by both CDP-12 and CDP-24 outcomes across two phase 3 studies versus IFNB-1a (Rebif) (see Table 23 of submission document B). ▪ The effect sizes of ocrelizumab compared with IFNB-1a (Rebif) for CDP-12 and CDP-24 are similar and demonstrate direct evidence of clinical benefit on disability progression. ▪ Further post hoc analyses of disability progression in the OPERA studies that extends the confirmatory period to 36 and 48 weeks (see Table 1 in Roche ACD response Appendix) demonstrates that ocrelizumab significantly reduces the risk of disability progression compared with IFNB-1a (Rebif) regardless of length of confirmatory period, and that there appears to be a trend for increasing effect sizes with longer confirmatory periods. CDP-36 and CDP-48 are not reported for other comparators hence an indirect treatment comparison could not be implemented in the economic analysis. However, the directional effect could be expected to result in more favourable incremental cost-effectiveness ratios (ICERs) for ocrelizumab. ▪ The committee concluded that beta-interferons and glatiramer acetate could be considered similar in terms of effectiveness (ACD page 6), hence the results of ocrelizumab versus IFNB-1a (Rebif) in the OPERA studies could be considered generalizable to all beta-interferons and glatiramer acetate. A mixed treatment comparison (MTC) is required to compare ocrelizumab with DMTs other than IFNB-1a (Rebif). As stated in the submission, the MTCs for CDP-12 were considered more robust than those for CDP-24 due to the better quality and quantity of data informing the CDP-12 network of evidence. The credible intervals for the CDP-24 MTCs were also wider due to added uncertainty which complicates drawing of conclusions. Although we agree with the committee that	considered the updated mixed treatment comparisons using model 1 and model 2, it noted the limitations in the subgroup data and recognised that some of the previous uncertainties had not been resolved by the updated models including, that data for the whole relapsing remitting population were used where data were not available for the subgroups. However, it considered that the updated models made the best use of the available evidence and could be used for decision making. The FAD has been amended to reflect this – see FAD section 3.10.

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			longer confirmation periods are generally better measures of sustained progression, the precision in the effect size and quality of indirect comparisons is also a function of the size and quality of the trials and available evidence. To bridge the difference in effect sizes observed in the CDP-12 and CDP-24 MTCs, the committee preferred to see joint modelling of CDP-12 and CDP-24, with missing CDP-24 data imputed based on CDP-12 data. Thus, Roche have conducted additional analyses using two different methods: • Model 1: CDP-24 analysis which uses CDP-12 input from any trial that did not report CDP-24 input (see Figure 1 in Roche ACD response Appendix). This method, which leads to one CDP output per treatment, was used in the most recent Cochrane review in RRMS [1] and by the Institute for Clinical and Economic Review (ICER) in their MS report published in 2017 [2]. • Model 2: a multivariate model allowing for the relative effects between non-placebo interventions to be exchangeable across outcomes, i.e. by allowing for inference to be made on both measures for comparisons where only one measure is available. This model, adapted from a model developed by Achana and colleagues [3], estimates two CDP effects, one for CDP-12 and one for CDP-24, which are strongly related given the assumptions made by the modelling approach. The results of the new MTC Model 1 suggest that ocrelizumab is more effective than placebo and five of the comparator treatments relevant to the NICE scope – IFNB-1a (Avonex), IFNB-1a (Rebif), IFNB-1b (Betaferon), glatiramer acetate, and teriflunomide (see Figure 2 in the Roche ACD response Appendix). There is no evidence of a statistical difference between ocrelizumab and dimethyl fumarate, fingolimod, natalizumab, alemtuzumab, and pegIFNB-1a as the credible intervals cross 1. The hazard ratios for ocrelizumab versus other comparators in MTC Model 1 typically fall (by point estimate) somewhere between the original CDP-12 and CDP-24 MTCs (see Figure 3 in the Roche ACD response Appendix). The credible intervals are noticeably narrower for new MTC Model 1 than for the original CDP-24 MTC. The results of the new MTC Model 2 suggest that ocrelizumab is more effective than placebo and seven of the comparator treatment relevant to the NICE scope – IFNB-1a (Avonex), IFNB-1a (Rebif), IFNB-1b (Betaferon), glatiramer acetate, teriflunomide, dimethyl fumarate, and fingolimod (see Figure 4 in Roche ACD response Appendix). There is no evidence of a statistical difference between ocrelizumab and natalizumab, alemtuzumab, and pegIFNB-1a as the credible intervals cross 1.	

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			The point estimates for ocrelizumab versus comparators were typically improved and the credible intervals were noticeably narrower for the new MTC Model 2 than for the original CDP-24 MTC. The revised base case economic analysis uses the new MTC Model 1, as this was considered more credible as it has been used by reputable institutions like Cochrane and ICER, and is also more conservative than the complex Model 2 method which is presented as scenario analysis only in the Roche ACD response Appendix. These results - both from direct evidence with further analysis of CDP-36 and CDP-48 in the OPERA studies and from indirect comparisons using two new MTC methods that jointly model CDP-12 and CDP-24 as requested by the committee - further strengthen the argument that ocrelizumab slows disability progression in the whole RRMS population.	
3	Consultee	Roche	**Subgroups** The ACD states in 3.10 that *'the mixed treatment comparison results are highly uncertain in the highly active and rapidly evolving severe subgroups.'* It also states in 3.11 that '*the committee was aware that the company had included data for the total relapsing–remitting population in the subgroup population networks because data were not available for the population of interest. The committee would have preferred these studies to have been excluded from the network when missing data could not be jointly modelled.'* Roche agree with the Committee and the ERG that there is considerable uncertainty in the subgroup MTC due to the sparsity of data. This is mainly due to the lack of subgroup data published for IFNB-1a (Rebif), IFNB-1a (Avonex) and placebo, i.e. treatments which connect ocrelizumab to the relevant comparators fingolimod and natalizumab, resulting in a disconnected network. For this reason, Roche proposed to use the ITT network as the basis for decision making. In order to connect the network, Roche have had to resort to using ITT data for these nodes under the assumption that there is no treatment effect modification between treatment and subgroup, as is the case in the OPERA trials. As requested by the committee, joint modelling of CDP-12 and CDP-24 was conducted for the HA and RES subgroups using the new MTC Model 1 approach, consistent with approach taken for ITT analysis (see Roche ACD response Appendix). The subgroup results are associated with wider credible intervals than the ITT results due to smaller sample size in subgroups and sparsity of subgroup data. The results suggest, for this reason, that there is no statistical difference between ocrelizumab and fingolimod and alemtuzumab in the HA subgroup, or between ocrelizumab and natalizumab and alemtuzumab in the RES subgroup.	Thank you for your comment. The committee acknowledged the lack of subgroup data available and considered that the updated networks made the best use of the available evidence. The FAD has been amended to reflect this – see FAD section 3.10.

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			Uncertainty in the subgroup MTCs, attributed to factors other than ocrelizumab's package of evidence from two double-blind, double-dummy RCTs compared to an active and appropriate comparator which shows consistent results in ITT and HA and RES subgroups on all major endpoints, should not detract from making a decision about ocrelizumab within its marketing authorisation.	
4	Consultee	Roche	**Safety profile** The ACD states in 3.12 that *'adverse events with ocrelizumab are broadly similar to those with other disease-modifying therapies.'* Roche do not agree with this statement and believe it needs contextualisation. In addition, it appears to be inconsistent with what the Committee concluded in 3.12: '*the adverse events were likely to be less frequent with ocrelizumab than with other similar therapies, including alemtuzumab*.' Roche would argue that the paragraph heading needs to specify that adverse events with ocrelizumab are broadly similar to those with moderate-efficacy therapies, but less frequent and less severe than those associated with other high-efficacy treatments. This is further supported by the distinct lack of monitoring with ocrelizumab as compared with the onerous monitoring burden of other high-efficacy treatments. Roche have acknowledged the committee's recommendations to include risk of PML in the model, but would like to highlight this remains a potential, rather than actual, risk. Given that there have been no reported cases of de novo PML causally attributed to ocrelizumab to date[1], the model used the PML rate from a cumulative analysis of confirmed PML cases in patients receiving rituximab in rheumatoid arthritis as a proxy. This information was based on both spontaneous reports and clinical trial sources as captured in the manufacturer global company safety and clinical databases indicating 2.56 PML cases per 100,000 patients over a period of 9-years [6]. It should be noted that these cases were typically associated with confounding PML risk factors, including prior and concomitant immunosuppressive therapies, unlikely to be present in MS patients. This cumulative rate was annualised (0.00028%) before application in the model.	Thank you for your comment, please see section 3.13 of the FAD, it has been amended accordingly for clarity. The committee considered that the annual rate of PML for ocrelizumab was likely to be much lower than for natalizumab (2.1%), but the length of follow up in the OPERA I and II trials is not yet long enough to assume that there is no risk of PML. It noted that economic scenario analyses had shown that the annual rate of PML does not have a big impact on the overall results. The committee agreed that the company's updated economic model using data based on rituximab could be accepted for decision-making. The FAD has been amended to reflect this – see FAD section 3.18.
5	Consultee	Roche	**Innovation** The ACD states in 3.25 that *'ocrelizumab is not innovative. The committee was*	Thank you for your comment. The committee considered that innovation had been adequately captured for ocrelizumab in the economic model, the

[1] As of April 2018, two cases of confirmed PML have been reported in two patients treated with ocrelizumab in the post-marketing setting. Both cases were reported as carry-over PML, meaning that both cases were confounded by prior treatment (natalizumab and fingolimod, respectively) before starting treatment with ocrelizumab. Natalizumab is associated with an increased risk of PML while on treatment and following discontinuation and there have been cases of PML reported with fingolimod in the post-marketing setting. [4. Biogen Idec Ltd. 2016, 5. Novartis Pharmaceuticals UK Ltd. 2015.]

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			aware that this was not the first treatment directed at the B-lymphocyte antigen CD20 for multiple sclerosis. However, it was the first to be licenced for the whole relapsing–remitting multiple sclerosis population. It heard from clinical experts that they considered it to have a better safety profile than some other high-efficacy treatments and therefore people with relapsing-remitting multiple sclerosis would need less frequent monitoring compared with other treatments such as alemtuzumab. It also has a low frequency of infusions, which people with relapsing-remitting multiple sclerosis value. Further, it appears to delay progression to secondary progressive multiple sclerosis. The committee recognised that some benefits relating to improvements in EDSS may not have been adequately captured in the modelling. However, it concluded that there is not enough evidence that ocrelizumab is innovative compared with other recent treatment options.' Roche are particularly concerned by the notion of ocrelizumab not being considered innovative. Ocrelizumab offers a unique combination of efficacy, safety, tolerability and convenience (via both low frequency of infusions and less frequent monitoring than other treatments). This combination of features is not matched by any other licensed DMT for the treatment of RRMS, as profiles of previous DMTs have demonstrated a trade-off between these factors, such that high-efficacy treatments are typically associated with a less favourable safety profile, dosing or monitoring, and vice versa. As heard in the first Appraisal Committee Meeting, the above points combined can have a significant impact on patients living with RRMS. The committee also recognised that some benefits relating to improvements in EDSS may not have been adequately captured in the modelling. Ocrelizumab is one of the very few DMTs demonstrating an effect on confirmed disability improvement, and the lack of inclusion of this benefit in the model confirms that the presented revised base case is conservative. Ocrelizumab is the first licensed anti-CD20 therapy in MS and rituximab [which we assume the committee referred to] was only ever studied in a dose-finding phase 2 study in RRMS and is not licensed for the treatment of MS. Ocrelizumab and rituximab differ in their structure (humanized versus chimeric antibody), and as a consequence there are anticipated differences in their immunogenicity, safety, and efficacy profiles [7-9]. Roche conclude that ocrelizumab in the context of other currently licenced and reimbursed high-efficacy options, should be considered an innovative treatment for RRMS and would invite the committee to reconsider its conclusion in the ACD in this regard.	FAD has been amended to reflect this – see FAD section 3.23.
6	Consultee	Roche	**Individual comparison to beta-interferons and glatiramer acetate**	Thank you for your comment. The committee considered the analyses comparing each individual

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			The ACD states in 3.4 that '*individual comparisons of ocrelizumab with beta interferons and glatiramer acetate are appropriate. The committee noted that, in the ongoing appraisal of beta interferons and glatiramer acetate for treating multiple sclerosis, it had concluded that the beta interferons and glatiramer acetate could be considered similar in terms of effectiveness but not in terms of cost effectiveness.'* To ease decision making, Roche have presented the revised base case based on the 'Cochrane' MTC for individual comparisons as requested in the appendix. These results demonstrate that ocrelizumab is a cost-effective use of NHS resources. Hereby Roche address the only outlier result that needs further explanation. The CDP-24 MTC results for pegIFN-1a suggest that it is more effective than other beta-interferons or glatiramer acetate, and similarly potent to high-efficacy treatments like natalizumab (see Figure 18 of submission document B). This lacks face validity and is contrary to clinical experience with pegIFNB-1a and clinical consensus about equivalence between beta-interferons and glatiramer acetate (as similarly concluded by the committee). Indeed, the EPAR for pegIFNB-1a comments on the unconventional definition of CDP in the single study informing the pegIFN-1a result in the network, and states that post hoc analysis using the conventional CDP-24 definition resulted in smaller effect sizes (post hoc results were not reported in the EPAR) [10]. As this outlier pegIFNB-1a result unreasonably affects the incremental analysis, Roche have presented the incremental analysis of the revised base case excluding pegIFNB-1a. However, additional analyses including pegIFNB-1a are presented in the Roche ACD response Appendix for transparency. Two new scenario analyses are also presented in the Appendix: 1) using the new MTC Model 2 which resolves some of the discrepancy observed in the pegIFNB-1a CDP-24 data (see Figure 4 in Roche ACD response Appendix), and 2) applying efficacy from trial comparator IFNB-1a (Rebif) to all beta-interferons and glatiramer acetate to reflect the committee's conclusion that these treatments are clinically equivalent. The latter scenario only varies the costs of drug, administration, monitoring, and AE management, and applies individual all-cause discontinuation rates from the MTC. This scenario analysis has the advantage of making use of the most robust evidence from two head-to-head studies comparing ocrelizumab with IFNB-1a (Rebif), and is in keeping with the committee's conclusion that beta-interferons and glatiramer acetate have similar effectiveness but not cost effectiveness. Both new scenario analyses indicated broadly similar results as the revised base case, and thereby support the robustness of the new base case.	beta-interferon and glatiramer acetate to ocrelizumab. It noted that pegylated interferon beta-1a appeared to be an outlier in terms of clinical effectiveness in the mixed treatment comparison for the outcome of confirmed disability progression. The FAD has been amended to reflect this – see FAD sections 3.10 and 3.11.

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7	Consultee	Roche	**Waning of treatment effect** The ACD states in 3.19 that *'treatment efficacy is likely to wane over time with ocrelizumab.'* It also states that *'the company was unable to provide the committee with evidence of an association between the presence of antibodies and treatment efficacy. The clinical experts explained that they would expect the efficacy of most treatments for multiple sclerosis to wane over time, either because the immune system develops neutralising antibodies that may prevent the treatment from working, or because the disease worsens.'* By definition, neutralising antibodies neutralise the biological effect of the antigen, therefore it would be anticipated that these would have a negative impact on the potential efficacy of treatment. Indeed, there is a wealth of evidence in the literature correlating the presence of neutralising antibodies with reduced efficacy of other DMTs in MS [11-16]. Therefore, the evidence confirms that neutralising antibodies are associated with treatment waning. As such, the negligible proportion of ocrelizumab patients developing anti-drug antibodies suggests neutralising antibodies cannot be a source of treatment waning for ocrelizumab. Additionally, Roche would like to reiterate the evidence initially presented in the manufacturer's submission supporting the notion that there is a low probability of long-term treatment waning with ocrelizumab: • Reduced immunogenicity of ocrelizumab vs. other biological MS DMTs reducing the probability of long-term waning due to formation of neutralising antibodies • Open label extension data demonstrating durable effects on both clinical and MRI disease activity up to 4 years Roche have maintained in the economic model all-cause discontinuation rates as requested by the committee, however do consider this a conservative assumption as a proxy for treatment waning as patients could withdraw from treatment for various reasons including tolerability. Patients withdrawing from treatment revert back to natural history of disease progression of untreated patients, and no longer accrue a treatment benefit in the economic model.	Thank you for your comment. The committee acknowledged that there are data to support no treatment waning effect for ocrelizumab in the frequency of relapses up to 4 years (FAD section 3.19), however there are no data beyond this. The committee accepted that treatment stopping could be considered a proxy for treatment waning in the absence of evidence (FAD section 3.20).
8	Consultee	Roche	An updated base case is provided in response to this ACD which reflects the committee's preferences, as discussed above. In addition, a number of scenario analyses have been conducted as supportive evidence (as also discussed in earlier sections of this response). Full details can be found in the Roche ACD response Appendix; however, a summary is provided below. Finally, Roche has updated the discount of ocrelizumab, to [redacted], equating to a	Thank you for your comment. The committee considered the results of the updated economic analyses, the FAD has been amended to reflect this – see sections 3.21 to 3.22.

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			300 mL vial price of [redacted] and yearly price of [redacted]. All with-PAS results in the appendix account for this new discount. New base case analysis The updated base case results in a QALY gain of [redacted] and a life-year gain of [redacted] for ocrelizumab. The resulting incremental ICER for ocrelizumab compared with glatiramer acetate is £21,720 based on the new PAS for ocrelizumab. This is based on exclusion of alemtuzumab to allow patient choice and exclusion of peg-IFNB-1a due to widely accepted outlier result. The ICERs for ocrelizumab versus beta-interferons and glatimar acetate range between £12,674 and £21,720. The base case results can be considered conservative because the treatment effect of ocrelizumab on disability improvement and on the longer disability progression outcomes CDP-36 and CDP-48 were not captured in the model. New scenario analyses Additional scenario analyses explored the impact of using the MTC Model 2 method to impute CDP-24, and of applying IFNB-1a (Rebif) efficacy results to all other beta-interferons and glatiramer acetate in line with the committee's conclusion of clinical equivalence between these treatments. In the latter scenario – which is preferable due to its simplicity, transparency, and in line with committee's assumptions – ICERs for ocrelizumab range between £12,674 and £26,283 per QALY versus the beta-interferons and glatiramer acetate, including pegIFNB-1a. The new scenarios resulted in broadly similar results as the revised base case, with ICERs for ocrelizumab versus beta-interferons and glatiramer acetate remaining well under the £30,000 per QALY threshold in all cases, and thereby supporting the robustness of the new base case. Subgroup analyses Subgroup analyses were conducted reflecting the committee's preferences and the revised PAS. When allowing patient choice and excluding alemtuzumab, ocrelizumab dominates fingolimod (based on list price) in the HA subgroup. Compared with natalizumab in the RES subgroup, ocrelizumab is estimated to be marginally less effective and much less costly than natalizumab. The subgroup results indicate that ocrelizumab is also a cost-effective treatment option in the HA and RES subgroups. Whilst the Patient Access Schemes associated with some of the comparator are not known to Roche, we hope the committee are satisfied with the updated	

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			analyses to deem ocrelizumab a cost-effective option within its marketing authorisation.	
9	Consultee	Association of British Neurologists	Commenting on behalf of the Association Of British Neurologist Advisory Group on Neuro-inflammation, I must express our disappointment at the rejection of the use of Ocrelizumab for Relapsing remitting multiple sclerosis. We believe it has the advantages of a unique mechanism of action among licensed drugs.It is one of the most highly effective at reducing relapses, reducing active lesions on MRI and on disability progression . It has a better overall safety profile than other highly active drugs. The risk of PML being much less than with Natalizumab. The risk of auto immune disease is much less than Alemtuzumab. The practicality of 6 monthly infusion versus every 28 days, while maintaining the ability to stop infusions if there is a medical need or patient falls pregnant is valuable. It will also be less costly. It does not require the 48 month blood and urine tests needed following a course of Alemtuzumab. As it is more specific to B cells it is not so generally immunosupressant as Cladribine.	Thank you for your comment. The committee considered that the benefits of ocrelizumab had been adequately captured in the economic model, including adverse events, administration, costs and efficacy. See section 3.23 of the FAD for further details.
10	Consultee	Association of British Neurologists	The committee was concerned that the risk of PML might be similar to that of Natalizumab. However the widely used anti CD20 antibody- Ritixumab is a more legitimate comparator. Clifford et al Arch Neurol 68(9) 1156-1164 form 2011 reported only 4 cases in 129,000 people treated of Rheumatoid arthritis, estimating a risk of 1 in 25,000. Whereas for Nataizumab the risk rises as high as 1 in 100 in JCV positive patients treated for several years. Although there has been one case of PML in someone with Ocrelizumab following on from Natalizumab and one now reported following on from fingolimod there have been none so far in those solely treated with ocrelizumb for their MS	Thank you for your comment. The committee considered that the annual rate of PML for ocrelizumab was likely to be much less than with natalizumab (2.1%), it noted updated analyses provided by the company including an annual risk of PML for ocrelizumab of 0.00028% based on data for rituximab. The company's updated annual rate was accepted for decision making. The FAD has been amended to reflect this – see FAD section 3.18.
11	Consultee	Association of British Neurologists	The committee might also consider the excellent retention and efficacy of off licence use of Ritizumab. The Swedish registry data suggests the 24% of 494 people with relapsing MS had both better efficacy and were more likely to remain on treatment than other fist line drugs. Granqvist et al JAMA 75(3) 320-327 2018. In part this will be due to the 6 monthly dose regimen. Ocrelizumab has a 6 monthly infusion regimen, additionally has phase 3 trial data of high efficacy.	Thank you for your comment.
12	Consultee	Association of British Neurologists	Highly effective drugs for MS have a greater beneficial effect in aggressive MS as they prevent more disabling relapses and more disability accrual. Although only 3 and 6 month disability progression was considered in the OPERA 1 and OPERA 2 studies a potential effect on the neurodegenerative aspect of MS can be extrapolated form the ORATORIO study in primary progressive MS where as well as 12 week disability progression 24 week disability progression was also superior to placebo.	Thank you for your comment, the committee concluded that ocrelizumab reduces relapses compared with all comparators apart from alemtuzumab. See FAD section 3.7.
13	Consultee	Association of British Neurologists	NICE may be aware that the Association of British Neurologists has recently developed a treatment algorithm together with NHS England to guide management of relapsing Multiple sclerosis. This is out for consultation. The potential place of Ocrelizumab in this treatment algorithm is worth consideration.	Thank you for your comment.

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14	Consultee	Department of Health and Social Care	No comment	Thank you for your response.
15	Consultee	MS Society	**Summary** The Committee acknowledge within the appraisal consultation document that ocrelizumab would be welcomed by people with MS who would value a treatment with less frequent dosing and monitoring requirements but concluded that they did not consider it as providing unique benefits compared with other treatment options. The MS Society strongly disagrees with this opinion and asks the Committee to take into full consideration the views and experiences of people with MS that were expressed at the committee meeting and in our previous submission. Ocrelizumab has been shown in clinical trials to be a highly effective treatment for relapsing MS and its 6 monthly infusion and side effect profile would make it the treatment of choice for many people with MS. Since the appraisal consultation document has been published we have been contacted by a number of people who have been advised by their neurologists that ocrelizumab would be better suited to their MS than other available treatments. They are concerned that they will no longer be able to access ocrelizumab and have written to describe why they think they would benefit.	Thank you for your comment. The committee considered the patient perspectives alongside the evidence on clinical and cost effectiveness. It concluded that the benefits of ocrelizumab had been adequately captured in the economic model, including adverse events, administration, costs and efficacy. See section 3.23 of the FAD for further details.
16	Consultee	MS Society	**Mode of Delivery** At the committee meeting, the patient experts gave oral evidence stressing that ocreliizumab had substantially improved their quality of life. The 6 monthly infusions have meant they have been free from the side effects and obligations involved with taking a treatment with a more frequent dosing schedule. The patient experts at the committee meeting had previously taken beta interferons to treat their MS and the benefit of not having to take frequent injections was noted by both. More people with MS who are taking ocrelizumab have since written to us expressing what a substantial impact less frequent administration and monitoring has had on their life, one individual commented “No longer having my day to day life run by medication means I'm able to have a normal life. You simply cannot put a price on that by itself.” This comment was from someone who had previously been taking dimethyl fumurate, taking two tablets a day. For people who alternatively would be taking daily tablets ocrelizumab has allowed them to engage in activities which were previously difficult. This includes socialising, holidays and not having to plan daily activities around taking medication. The committee should take into account the improved quality of life which comes with a much less onerous treatment schedule.	Thank you for your comment. The committee considered the patient perspectives alongside the evidence on clinical and cost effectiveness – see FAD sections 3.1 and 3.3.
17	Consultee	MS Society	**Side Effects**	Thank you for your comment. The committee considered the importance of taking into account

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			The committee acknowledges that adverse events are less likely to be experienced with ocrelizumab than with other MS treatments and that though the risk of PML cannot be ruled out it is 'likely to be lower than natalizumab'. We have heard from people who are currently taking natalizumab who have been told they are at high risk of contracting PML. They have told us that they would like the opportunity to take ocrelizumab instead and are concerned that they will now not be able to. One person who is on natalizumab explained that she has been waiting for ocrelizumab to be approved for over a year and that while natalizumab is controlling her MS, she feels that she is playing 'russian roulette' every time she has an infusion. 'I had an extreme allergic reaction to Tysabri so was put onto a less effective DMT with the hope that if I relapsed on that, in the future Ocrelizumab would be an option.' - Person with MS. The clinical experts explained that ocrelizumab would likely be used as a first line therapy option for those who are unable to tolerate the side effects of alemtuzumab and that they considered to have a better safety profile than other high-efficacy treatments. This means there would be a clear place for ocrelizumab within the treatment pathway for relapsing MS. The potential side effects for alemtuzumab range from thyroid and kidney problems to idiopathic thrombocytopenic purpura (ITP) which causes many people concern before starting treatment.	patient preferences when making shared decisions about treatment. The FAD has been amended to reflect this – see FAD section 3.3.
18	Consultee	MS Society	**Innovation** The committee concluded that ocrelizumab should not be considered an innovative treatment despite it being the first licensed drug for MS which targets B-cells. We strongly disagree with this conclusion. People with MS react differently to different treatments, the more options available which have different mechanisms will result in more people finding the treatment which works best at tackling their MS.	Thank you for your comment. The committee considered that innovation had been adequately captured for ocrelizumab in the economic model, the FAD has been amended to reflect this – see FAD section 3.23.
19	Consultee	MS Society	**Treatment Waning** The committee has applied a treatment waning effect to ocrelizumab over time without clear evidence to support this. While they may feel that there is not enough evidence to support the model laid out by the company they in turn cannot provide evidence to support that ocrelizumab treatment effect will wane over time to the degree assumed. The committee say that the company's assertion that there were less anti-drug antibodies in the ocrelizumab group was not backed up by evidence of an association between the presence of antibodies and treatment efficacy. However, they also say that treatment waning is likely due to the immune system developing neutralising antibodies. Without evidence to support this claim, the committee is applying one rule to the company and another to itself.	Thank you for your comment. The committee acknowledged that there are data to support no treatment waning effect for ocrelizumab in the frequency of relapses up to 4 years (FAD section 3.19, however there are no data beyond this. The committee accepted that treatment stopping could be considered a proxy for treatment waning in the absence of evidence (FAD section 3.20).

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20	Consultee	MS Society	**Costs to NHS** Ocrelizumab is likely to reduce additional costs to the NHS due to the number of people who would choose ocrelizumab over natalizumab. The less frequent administration and less arduous monitoring would mean less additional NHS resources would be required. This should be fully considered when weighing up ocrelizumab's cost effectiveness.	Thank you for your comment. The perspective on costs in the economic model was considered from an NHS and PSS perspective as stipulated by the reference case, see the guide to the methods of technology appraisal section 5.1.
21	Consultee	Multiple Sclerosis Trust	The MS Trust is extremely disappointed that ocrelizumab is not recommended for relapsing forms of multiple sclerosis in adults with active disease defined by clinical or imaging features.	Thank you for your comment.
22	Consultee	Multiple Sclerosis Trust	**Innovative nature of ocrelizumab** In reviewing the innovative nature of ocrelizumab, the committee concludes that there is not enough evidence that ocrelizumab is innovative compared with other treatment options (3.25). **We strongly disagree with this assessment.** To demonstrate the innovative nature of ocrelizumab, we have compared ocrelizumab to disease modifying drugs with a similar degree of effectiveness: natalizumab, fingolimod and alemtuzumab.	Thank you for your comment. The committee considered that innovation had been adequately captured for ocrelizumab in the economic model, the FAD has been amended to reflect this – see FAD section 3.23.
23	Consultee	Multiple Sclerosis Trust	• **Novel mechanism of action** Ocrelizumab is the first licensed treatment directed at the B-lymphocyte antigen CD20 for MS. It is the first humanized CD20 monoclonal antibody so it is expected to be less immunogenic with repeated infusions. Through a variety of different mechanisms of action, each of the other disease modifying drugs acts via T-lymphocytes. There is increasing research evidence that B-lymphocytes, particularly B memory cells, play a pivotal role in the pathogenesis of MS, so ocrelizumab represents a highly targeted approach to treatment.	Thank you for your comment, the committee acknowledged that ocrelizumab is the first B-lymphocyte antigen CD20 to be licensed for the whole relapsing–remitting multiple sclerosis population - see section 3.23 of the FAD.
24	Consultee	Multiple Sclerosis Trust	• **Convenient six monthly dosing schedule** Ocrelizumab offers a novel treatment schedule, aiding adherence, minimising impact on NHS infusion services and reducing the burden of treatment for patients. Both patient and clinical experts emphasised in their written submissions and at the committee meeting the benefits of less frequent hospital visits. Treatment burden: • Ocrelizumab: 2 infusions/year. • Natalizumab: 12 infusions/year. This has a significant impact on NHS infusion services, and for the patient requires frequent visits to hospital, which leads to time away from work or family commitments and often lengthy and costly	Thank you for your comment. The committee considered that the benefits of ocrelizumab had been adequately captured in the economic model, including adverse events, administration, costs and efficacy. See section 3.23 of the FAD for further details.

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			journeys. The need for monthly treatments can have further practical implications, for example for someone planning extended overseas travel. • Fingolimod: 365 tablets/year. Offers convenience of self-treatment at home, but adherence can be a problem since people often forget to take fingolimod on a regular basis. Problems with home delivery of medication can be very frustrating and time-consuming, adding to the burden of treatment. • Alemtuzumab: two treatment courses, infusions for five consecutive days in year 1, infusions for three consecutive days twelve months later. In addition, patients must avoid exposure to infections, in particular avoid foods that may be a source of Listeria two weeks before, during and one month after treatment. Patients often feel very unwell for some weeks after treatment, needing to take time off work and are unable to carry out family responsibilities. Furthermore, we understand that NHS England is currently refusing to fund a third course of alemtuzumab for people with breakthrough disease. As the five year follow-ups alemtuzumab clinical trials reported that nearly half of the participants received retreatment, the refusal to fund a third course is a significant concern for both clinicians and patients and adds to treatment burden.	
25	Consultee	Multiple Sclerosis Trust	• **Low risk of side effects** A combination of high efficacy and low level of serious side effects makes ocrelizumab an attractive alternative to other highly effective disease modifying drugs. Side effects: • Ocrelizumab: infusion reactions; respiratory tract infections; herpes infection; hepatitis B reactivation; neutropenia; very low risk of progressive multifocal leukoencephalopathy (PML). • Natalizumab: higher risk of PML - serious, potentially fatal, brain infection caused by reactivation of JC virus, increased risk after 2 years of treatment; infusion reactions; liver problems; severe allergic reaction during infusion • Fingolimod: cardiac problems on first dose; herpes infection; liver enzyme problems; lymphopenia; macular oedema; basal cell carcinoma; opportunistic infections; low risk of PML • Alemtuzumab: infusion reactions; opportunistic infections; thyroid problems; idiopathic thrombocytopenic purpura; kidney problems	Thank you for your comment. The committee considered that the benefits of ocrelizumab had been adequately captured in the economic model, including adverse events, administration, costs and efficacy. See section 3.23 of the FAD for further details.
26	Consultee	Multiple Sclerosis Trust	• **Minimal monitoring requirements** The low level of side effects with ocrelizumab is reflected by minimal requirement for monitoring. This reduces pressure on NHS resources and is very much more convenient for patient. Monitoring burden:	Thank you for your comment. The committee considered that the benefits of ocrelizumab had been adequately captured in the economic model, including adverse events, administration, costs and efficacy. See section 3.23 of the FAD for further details.

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			• Ocrelizumab: hepatitis B screening before first dose; no requirement for blood or urine tests or other routine monitoring • Natalizumab: annual MRIs; six-monthly blood tests for JC virus while virus levels negative or low • Fingolimod: cardiovascular monitoring with first dose; before first dose check chickenpox status and vaccinate if necessary; regular blood tests; eye test at 3-4 months after starting treatment; annual skin check • Alemtuzumab: monthly blood and urine tests for four years after last treatment course	
27	Consultee	Multiple Sclerosis Trust	**Cost effectiveness estimates** The committee notes a number of preferred economic analyses (3.21) and we trust that the manufacturer will provide these. We entirely recognise the importance of establishing cost effectiveness for a new treatment, but we feel that the appraisal process continues to be dominated by a very technical analysis of the economic model. This gives little opportunity for stakeholders with limited expertise in health economics to be able to participate and challenge assumptions. There is a danger of the appraisal process being consumed by hypothetical manipulation of the mathematical model and disconnected from the practical reality of clinical practice. This issue is further exacerbated by redaction of data at committee meetings and from the ACD. We understand the confidential nature of patient access schemes, but this makes it impossible for consultees to engage in discussions of cost effectiveness which are absolutely critical to decision making. Although cost effectiveness estimates take account of comparative costs of treatment and monitoring, they do not take account of supply of limited resources. Cost effectiveness estimates do not reflect the real-world impact of resourcing treatment and monitoring in the over-stretched NHS or the impact on people's lives. The lower level of monitoring and treatment required for ocrelizumab offer benefits for both the NHS and patients which cannot be captured by economic models.	Thank you for your comment. The views of clinical experts and patient/carer representatives were considered by the committee when formulating its recommendations. The potential budget impact of the adoption of a new technology does not determine the committee's decision. The committee does take account of how its advice may enable the more efficient use of available healthcare resources. In general, the committee will want to be increasingly certain of the cost effectiveness of a technology as the impact of the adoption of the technology on NHS resources increases." (from Guide to the methods of technology appraisal 2013, section 6.2.14). A costing report and template will be available when the guidance is published.
28	Consultee	Multiple Sclerosis Trust	**Treatment waning** There is no clinical evidence for treatment waning. The manufacturer has been very clear that ocrelizumab causes negligible levels of neutralizing antibody and that 4 year open label extension data shows sustained treatment efficacy. Treatment waning was introduced during the fingolimod appraisal (TA254). The manufacturer carried out a sensitivity analysis on their economic model to see	Thank you for your comment. The committee acknowledged that there are data to support no treatment waning effect for ocrelizumab in the frequency of relapses up to 4 years (FAD section 3.19), however there are no data beyond this. The committee accepted that treatment stopping could be considered a proxy for treatment waning in the

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			what would happen if there was a **hypothetical** treatment waning and, not surprisingly, the ICER increased. The concept of treatment waning is without precedent in previous MS NICE appraisals. Treatment waning is **hypothetical,** was used to test the responsiveness of a mathematical model and was not based on clinical observation. While we acknowledge that it is difficult to extrapolate two year clinical trial data to long term treatment, we wish to emphasise that there is **no clinical evidence to support loss of efficacy**. Moreover, there is no evidence to justify the arbitrary choice of discontinuation rates as a proxy for treatment waning. There are many factors influencing discontinuation rates, from intolerable side effects through differences in mode and frequency of administration to personal difficulties in attending a study centre; presumed treatment waning over a two year clinical trial is going to be one of the least likely reasons for discontinuing treatment. The ACD states (3.19, p15) "Clinical experts explained that they would expect the efficacy of most treatments for multiple sclerosis to wane over time, either because the immune system develops neutralizing antibodies that may prevent the treatment form working, or because the disease worsens". This is a reasonable, professionally cautious response to the Committee's question. However, the company has already noted that ocrelizumab causes negligible levels of neutralising antibodies; disease worsening is implicit in the economic model. The use of treatment waning in multiple sclerosis technology appraisals has become de facto, in the absence of clinical evidence or biological plausibility, the only purpose being to force an increase in the ICER. Unless this is a routine assumption for all drug technology appraisals, we consider this to be inequitable treatment for MS drugs and completely unjustified.	absence of evidence (FAD section 3.20).
29	Consultee	Multiple Sclerosis Trust	**Patient experience** **We do not feel that the advantages of ocrelizumab for people with MS have been adequately stated or taken into account in the ACD.** The appraisal consultation document does not reflect the very positive experience of patient experts expressed at the committee meeting and in submissions from patient organisations. At the committee meeting, a member of the committee directly asked the patient experts about their experience of ocrelizumab. One of the patient experts described how she was initially taking Rebif but found the flu-like side effects debilitating. On switching to ocrelizumab, she found the six-monthly treatment schedule much less burdensome, and experienced improvements in function and	Thank you for your comment. The committee considered patient perspectives when formulating its recommendations. See FAD section 3.1 for further details. It also considered the importance of taking into account patient preferences when making shared decisions about treatment. The FAD has been amended to reflect this – see FAD section 3.3.

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			cognition. In her own words: "I didn't realise how ill I was until I wasn't ill." The second patient expert stated that ocrelizumab had genuinely worked for her, she now leads a very normal life and doesn't consider herself to be disabled in any way.	
30	Consultee	Multiple Sclerosis Trust	**Conclusion** It is our view that ocrelizumab offers a unique combination of novel mechanism of action, convenient dosing schedule, low risk of side effects and minimal monitoring. This combination sets it apart from other disease modifying drugs and makes it a valuable additional treatment for people with relapsing remitting MS and for the NHS. Despite the overall effectiveness of disease modifying drugs for reducing frequency and severity of MS relapses, any one of them can simply fail to work in a particular patient, or cause debilitating side effects. Clinicians lack tools to predict who would respond well to a specific therapy. A wider range of therapies gives greater scope for personalised treatment. Research evidence demonstrates the importance of active, early treatment of relapsing remitting MS to prevent axonal damage and avoid irreversible disability. The EMA has licensed ocrelizumab because it is a highly effective, safe drug for people with relapsing MS. The difficulty in calculating cost effectiveness of MS drugs is well recognised, particularly as the trial data does not address the long-term benefits of treatment. People with MS in the UK are at risk of lagging even further behind other developed countries in their access to licensed drugs. The MS Trust encourages the Committee to recognise that ocrelizumab would be an important addition to the disease modifying drugs approved for relapsing remitting MS. As with other disease modifying therapies, ocrelizumab should be prescribed by neurologists, with commencement of therapy and ongoing monitoring provided by specialist MS nurses.	Thank you for your comment.
31	Clinical expert	Dr David Hunt	**Summary** I disagree with the conclusion that ocrelizumab does not offer unique benefits compared with other treatment options. People with MS, particularly active forms of MS, have an unmet need for safe, high efficacy treatments. Alemtuzumab and natalizumab are both recognised as high efficacy treatments, and it is recognised that ocrelizumab is a new third high efficacy option. There are people with active MS for whom natalizumab/alemtuzumab are not appropriate or contraindicated. For natalizumab, these are patients with evidence of JC virus infection, who are at long-term risk of PML. For alemtuzumab, these are patients who have other	Thank you for your comment. The committee considered that the benefits of ocrelizumab had been adequately captured in the economic model, including adverse events, administration, costs and efficacy. See section 3.23 of the FAD for further details.

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			autoimmune diseases, or concerns about developing secondary autoimmunity. These are patient groups for whom ocrelizumab would represent an important alternative high efficacy option.	
32	Clinical expert	Dr David Hunt	**Mode of Delivery** The mode of delivery of ocrelizumab offers important advantage over many current medications (Alemtuzumab – the large majority of patients have significant cytokine release syndrome reactions requiring careful monitoring. Natalizumab requires monthly infusions. Fingolimod requires intensive first dose monitoring with cardiac surveillance). Feedback from patients in clinic with MS/other autoimmune disease who receive 6-monthly infusions with rituximab (which has a similar dosing schedule to ocrelizumab) is typically positive, with patients finding this treatment regimen minimally intrusive for their daily lives, with no daily pill/injection and less frequent monitoring. This is concordant with the evidence given by patient experts receiving ocrelizumab therapy.	Thank you for your comment. The committee considered the importance of taking into account patient preferences when making shared decisions about treatment. The FAD has been amended to reflect this – see FAD section 3.3.
33	Clinical expert	Dr David Hunt	**Side Effects** The full side effect profile of ocrelizumab in the postmarketing setting remains to be established, and it is possible that signals including PML may occur in the early postmarketing setting. However, at this early stage it is reasonable to conclude that the level of PML risk will be favourable compared to natalizumab. Indeed, switching to anti-B cell therapies in natalizumab-treated patients at high-risk of PML has become established practice in a number of centres (Alping et al. Annals Neurology 2016 79 (6) 950-958). At the present time the side-effect profile of ocrelizumab appears to be favourable compared to other high efficacy drugs.	Thank you for your comment. The committee considered that the annual rate of PML for ocrelizumab was likely to be much less than with natalizumab (2.1%). It noted updated analyses provided by the company including an annual risk of PML for ocrelizumab of 0.00028% based on data for rituximab. The company's updated annual rate was accepted for decision making. The FAD has been amended to reflect this – see FAD section 3.18.
34	Clinical expert	Dr David Hunt	**Innovation** B-cell targeted therapies represent a novel mechanism of action in multiple sclerosis, compared to other licensed therapies.	Thank you for your comment, the committee acknowledged that ocrelizumab is the first B-lymphocyte antigen CD20 to be licensed for the whole relapsing–remitting multiple sclerosis population, see section 3.23 of the FAD.
35	Clinical expert	Dr David Hunt	**Treatment Waning** I disagree with the conclusions regarding treatment waning. I have seen no evidence in the course of the submission – or my own reading – which provides convincing evidence of this phenomenon. Real-world studies of early use of anti-B cell therapies (rituximab use in Swedish MS registry, Granquist et al. JAMA Neurol. 2018 Mar 1;75(3):320-327) are consistent with sustained efficacy of this drug class, and suggest superiority to other DMTs, including high efficacy drugs such as natalizumab.	Thank you for your comment. The committee acknowledged that there are data to support no treatment waning effect for ocrelizumab in the frequency of relapses up to 4 years (FAD section 3.19), however there are no data beyond this. The committee accepted that treatment stopping could be considered a proxy for treatment waning in the absence of evidence (FAD section 3.20).

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			I particularly disagree with the interpretation of my comments regarding neutralising antibodies While neutralising antibodies develop against almost all biologic agents, their role in negating of the effects of treatment are not always clear and should be considered a form of treatment failure. That is, the drug should be changed in those who develop such antibodies. In those patients who do not develop antibodies, I have seen no evidence of treatment waning. While there is consensus that immunotherapies are likely to be maximally efficacious when given early in the clinical course of multiple sclerosis, these comments should not be interpreted to suggest that, in an individual patient, treatment efficacy wanes over time.	
36	Clinical Expert	Dr Helen Ford	I am disappointed that ocrelizumab has not been recommended, within its marketing authorisation, for treating relapsing remitting MS. In my opinion it would be a useful addition to currently available treatment options for RRMS.	Thank you for your comment.
37	Clinical Expert	Dr Helen Ford	3.2: I am concerned that the interpretation of the clinical expert evidence was that the majority of patients would currently start treatment with an injectable DMT such as interferon or glatiramer acetate. Many patients start on a 'first line' DMT which includes the oral treatments dimethyl fumarate and teriflunomide. The use of first line injectable treatments has significantly reduced since the approval of the oral first line drugs.	Thank you for your comment. The FAD has been amended to reflect this - see FAD section 3.2.
38	Clinical Expert	Dr Helen Ford	3.12: The adverse events with ocrelizumab are not broadly similar to those with other DMTs. In the CARE-MS I (alemtuzumab) 5 year follow up the incidence of autoimmune thyroid events was 40.7% and in CARE-MS II 37.7%. Patients require monthly blood tests for 48 months from their last treatment with alemtuzumab. I'm not aware of any reports of autoimmune conditions following treatment with ocrelizumab. The overall risk of PML in patients with positive JC virus serology following treatment with natalizumab is greater than 4/1000. There have been no reported cases attributed to treatment with ocrelizumab and any risk is likely to be significantly lower than that associated with natalizumab.	Thank you for your comment. The FAD has been amended to reflect this - see FAD sections 3.13 and 3.18.
39	Clinical Expert	Dr Helen Ford	3.19: The clinical experts advised that patients on treatment with natalizumab can remain relapse free for years and only on stopping treatment eg for pregnancy does the disease re-emerge. This is against the concept of treatment waning. The clinical experts advised of the uncertainty of the role of neutralising antibodies in treatment waning. For anti-CD20 mAbs there has not been a consistent association between immunogenicity and lack of efficacy or adverse effects. For ocrelizumab immunogenicity was limited, with only 0.4%of ocrelizumab-treated patients in the two trials developing anti-drug antibodies.	Thank you for your comment. The committee acknowledged that there are data to support no treatment waning effect for ocrelizumab in the frequency of relapses up to 4 years (FAD section 3.19), however there are no data beyond this. The committee accepted that treatment stopping could be considered a proxy for treatment waning in the absence of evidence (FAD section 3.20).
40	Commentator	Novartis Pharmaceuticals UK Limited	Paragraph 3.11. Novartis is concerned about the validity of the novel approach to imputation of missing 6-month confirmed disability progression suggested in the ACD. The rationale for the Committee preferring 6-month to 3-month confirmed data is that patients not yet fully recovered from a recent relapse confound the 3-month data. Given that such confounding is expected to be random there is no *a priori* expectation that the ratio of 3:6 month data in any one study would be	Thank you for your comment. In response to consultation the company produced 2 new approaches to the mixed treatment comparison analyses for the outcome confirmed disability progression. The committee heard from the ERG that model 2 used 3 and 6 month data across the network to infer a

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			consistent with that in any other study of the same drug, unless both trials were sufficiently large in sample size so as to dilute the random error. It may be observed that most trials included in the networks are of 1 or 2 year duration and that trials of older drugs may have been powered to detect differences in relapses rather than 6-month confirmed disability progression. This assumption would become even more problematic in the highly active and rapidly evolving severe subgroups.	relationship between the two outcomes. This information was then used to generate missing data for CDP at 3 months and 6 months. The committee noted the assumptions made in both model 1 and model 2 and these were taken into consideration in their decision making. See FAD section 3.10 for further details.
41	Commentator	Novartis Pharmaceuticals UK Limited	Paragraph 3.12. Sentence beginning "The patient explained that…" It should be added that the patient was speaking about a specific interferon and that this statement is specific to that drug. Each drug has a distinct adverse event profile and this statement is not applicable across all drugs – in particular, this statement does not apply to non-interferon drugs.	Thank you for your comment. The FAD has been amended to reflect this – see FAD section 3.13.
42	Commentator	Novartis Pharmaceuticals UK Limited	Paragraph 3.13 onwards. It is not clear from the ACD whether the company approach of applying some clinical effectiveness to the transition from RRMS to SPMS was accepted by the committee or rejected as suggested by the ERG. It is important for transparency of decision making that this is recorded in the ACD.	Thank you for your comment. The committee noted that changing this assumption only had a small effect on the ICERs and therefore it did not express a preference for one approach over the other.
43	Commentator	Sanofi Genzyme	Sanofi Genzyme (SGZ) believes that all the relevant evidence has been considered, apart from data on the annualised relapse rate (ARR) in the highly active subgroup which was 0.18 for alemtuzumab (Krieger S *et al*. Neurology Apr 2016, 86 (16 Supplement) S51.003).	Thank you for your comment.
44	Commentator	Sanofi Genzyme	SGZ agrees with the committee that the preferred assumptions should include efficacy estimates for confirmed disability progression at 6 months (6CDP). Although there may appear to be correlation between CDP-12 and CDP-24 for ocrelizumab, this is based on the two OPERA studies only. The absence of data on other comparators to validate this, the assumption that CDP-12 and CDP-24 are highly correlated could lead to invalid conclusions.	Thank you for your comment. In response to consultation the company provided updated mixed treatment comparisons for confirmed disability progression at 6 months. The committee considered the limitations of these analyses in their decision making. See FAD section 3.10 for further details.
45	Commentator	Sanofi Genzyme	SGZ believes that the statement in section 3.25 of the ACD stating that ocrelizumab 'was the first to be licensed for the whole relapsing-remitting multiple sclerosis (RRMS) to be potentially misleading. Alemtuzumab is licensed for RRMS therefore we request that this statement is removed.	Thank you for your comment. The FAD has been amended for clarity – see FAD section 3.23.
46	Commentator	Sanofi Genzyme	SGZ agree with the committee that the same waning effect is applied to all comparators as in previous submissions.	Thank you for your comment.
47	Commentator	Sanofi Genzyme	SGZ acknowledges that patients who receive alemtuzumab may experience autoimmune diseases such as thyroid disorders. These autoimmune diseases are well known and predictable and in the majority of cases mild or moderate. For example thyroid disorders peak at year 3 (Coles 2017 Neurology). Serious events were reported in less than 2.5% each year and most thyroid events were managed with conventional medical therapy. Within the CARE MS studies, patients who developed thyroid events were permitted to receive re-treatment with alemtuzumab and although experience is limited, patients who were re-treated generally did not experience a worsening in severity of thyroid disorders as stated in the alemtuzumab SmPC. We would prefer the wording to say that 'patients having alemtuzumab experience predictable autoimmune diseases which requires	Thank you for your comment. The FAD has been amended for clarity – please see section 3.13.

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			monitoring for a finite period (48 months) after stopping treatment'' as per SmPC.	
48	Commentator	Sanofi Genzyme	SGZ agree that two additional courses of alemtuzumab should be modelled for cost-effectiveness as per SmPC. The CARE MS extension studies have demonstrated that alemtuzumab has a durable efficacy with the majority of patients, 63%, not requiring a re-treatment with alemtuzumab. The retreatment rates of alemtuzumab have been published with the retreatment rates in year 3, 4 and 5 being 19.3%, 15.8% and 12.5% respectively. These rates have been applied within the cost-effectiveness model. However, the calculation for year 5 onwards is not correct in the model. The annual rate applied after year 5 should be 6%. This is based on patients that have had a 3rd and 4th course in years 5 onwards from the real world follow up of 87 patients by Touhy et al. As it currently is in the economic model retreatment cycles are double counted in years 5 onwards. As per NICE process we have also provided similar comments on the economic model separately.	Thank you for your comment. The committee noted that, alemtuzumab dominated ocrelizumab in all of the company and ERG analyses. See FAD section 3.21.
49	Commentator	Sanofi Genzyme	SGZ would like to highlight that the question 26 raised within the NICE clinical expert statement and published part of the committee papers refers to alemtuzumab being immunosuppressive, which is also raised within the company submission. Research suggests that alemtuzumab exerts it effects in an immunomodulatory manner through the depletion and repopulation of lymphocytes, including: - Alterations in the number, proportions, and properties of some lymphocyte subsets post-treatment. - Increased representation of regulatory T cell subsets. - Increased representation of memory T- and B-lymphocytes. - Transient effects on components of innate immunity (i.e., neutrophils, macrophages, NK cells) Data from Kovarova ENS 2012, show mean B cell values approached baseline and reached the normal range by 3 months after each treatment course. Mean CD4+ T cell counts approached LLN, on average, 24 months after the last treatment course. Mean CD8+ T cell counts reached LLN ~9 months after treatment. The reduction in the level of circulating B and T cells and subsequent repopulation, suggests that alemtuzumab does not produce irreversible immunosuppressive effects, and may be the mechanism in which it reduces the potential for relapse, ultimately delaying disease progression. (https://www.medicines.org.uk/emc/product/5409). Additional data to support this immunomodulatory effect can be found in the following references, Coles Lancet 2012, Hartung 2012 and Kasper 2013. The CARE MS extension studies also indicate a low incidence of infections and serious infections further supporting the lack of an immunosuppressive effect. We ask NICE to consider this	Thank you for your comment.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			when preparing any future ACD/FAD for DMTs within MS.	
50	Commentator	Sanofi Genzyme	Comments on economic model Description of problem Retreatment rates applied in the model for alemtuzumab post 5 years Description of proposed amendment SGZ agree that two additional courses of alemtuzumab should be modelled for cost-effectiveness as per SmPC. The CARE MS extension studies have demonstrated that alemtuzumab has a durable efficacy with the majority of patients, 63%, not requiring a re-treatment with alemtuzumab. The retreatment rates of alemtuzumab have been published with the retreatment rates in year 3, 4 and 5 being 19.3%, 15.8% and 12.5% respectively. These rates have been applied within the cost-effectiveness model. However, the calculation for year 5 onwards is not correct in the model. The annual rate applied after year 5 should be 6%. This is based on patients that have had a 3rd and 4th course in years 5 onwards from the real world follow up of 87 patients by Touhy et al. As it currently is in the economic model retreatment cycles are double counted in years 5 onwards. Results of amended model or expected impact on the result Model was not re-run. As alemtuzumab currently dominates at the list price we do not expect this results to change, however it may change if a PAS price is used for ocrelizumab	Thank you for your comment. The committee noted that, alemtuzumab dominated ocrelizumab in all of the company and ERG analyses. See FAD section 3.21.
51	Public	Patient 1	I have MS and have been treated with alemtuzumab and 2 years after r2 I believe I have not relapsed. i believe that Â£56 000 is good value as it means I do not need monthly infusions for the rest of time, it is also low maintenance for the nhs long term too. Now if the treatment starts to fail and I start relapsing again, would Ocrelizumab not be a good option to fall back and also this could be the same for people currently on tysabri etc.	Thank you for your comment.
52	Public	Patient 2	I've read on your website that Nice have initially rejected Ocrelizumab and this terrifies me. After diagnosis in 2015 following 2 relapses is quick succession where I lost pretty much all use in my left side for a couple months had some debilitating spasms and had to take 4 months off work I was put on Tecfidera. The side effects were not great to start with and I continued to relapse and had ongoing issues of fatigue, bladder and bowel problems and balance issues even when not relapsing. I was put on Ocrelizumab in June of last year under a trial and I cannot believe the difference it has made to my life. Firstly, being only every 6 months it is so less invasive on my day to day life. No longer ruled by tablets which made doing anything spontaneous almost impossible as my life had to be planned around taking tablets. Wanna go out for a few unplanned drinks after work? Nope! Have one then have to go home to eat and take tablets. Or constantly have to carry tablets around with you which I can tell you doormen do not like you taking	Thank you for your comment.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			into pubs / clubs. Wanna have a lie in? Nope! Get up and eat so you can take your tablets. No longer having my day to day life run by medication means I'm able to have a normal life. You simply cannot put a price on that by itself. But, on top of all that, my fatigue has almost vanished. I feel normal again. My work had improved as I'm no longer struggling to get through the day. I've not soiled myself once, and no longer feel the need to carry around a change of clothes 'just in case'. I've not had any bladder problems, no longer constantly looking for the nearest toilet or having to frequently use public facilities that are dirty. And I'm able to train in a gym. I'm going between 2 and 4 times a week and still have the energy to do things with my family. Before I would be too tired mostly after work to do much. Want a normal sex life? Before we had to pretty much plan it to ensure I had the energy as I used to be falling asleep as soon as I got home. Not now!!! You simply can't put a price on how my life has improved. Yes I still have bad days, I know I'm not cured but they are few and far between rather than being almost every day. But I've not relapsed once and this is the longest I've gone without relapsing since diagnosis. I'm fitter, stronger, healthier, happier, and I have a life. It's given me a NORMAL life where MS isn't the main thing in it. All the things people take for granted life having energy to for the things they want rather than just work and sleep, not carrying spare clothes everywhere. Not having life ruled by daily medication. Making plans, I had stopped making any plans before being on this drug cause most of the time I only ended up cancelling them but not now. I can honestly say I feel this drug has given me my life back. And that is why it really does terrify me that it hasn't been approved. What I am supposed to do after the trial I'm on finishes? Go back to having no normal life? Nice have to see that whilst there may be other drugs that also help slow down progression, it's also about quality of life. Being alive is a lot different to having a life that is wonderful. I cannot stress how much this has given me my life back. Sorry for going on a bit, but I'm honestly scared of having to come off this drug at the end of the trial, as is my husband as he can clearly see the difference in me. I don't want to lose my life again.	
53	Public	Patient 3	I was diagnosed with PPMS in 2013 and not given any treatment. In 2015, following a relapse it was decided I was RRMS and put on Tysabri. This worked well for me for 2 years until I was taken off due to rising JC virus levels. Since then I have been on Daclizumab and now Gilenya. My concern is what happens in a few years time when my current treatment stops working? I had been pinning my hopes on Ocrelizumab being available by then.	Thank you for your comment.
54	Public	Patient 4	Please as a sufferer of MS (SPMS) or Secondary Progressive Multiple Sclerosis I am asking that you do not stop this medication to be avalable via the NHS as it is helpful to people whom are newly diagnosed with MS. Thank you for your time and consideration	Thank you for your comment.
55	Public	Carer 1	While it is accepted that there are many DMT medications available for RRMS, many of which are fairly effective at reducing the risk of relapse, what they all have in common is that they can only protect against further relapse. Crucially what is different about Ocrelizumab is that is the first drug ever to show	Thank you for your comment.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			reduction in disability. It is the first and only drug to offer this type of hope to anyone with any form of MS. My daughter aged 45 suffers from RRMS. She uses pilates, physiotherapy and diet to hold back the effects of the disease as much as possible. In spite of her commitment and effort she has become much more disabled over the last year. Last year her consultant told her that she would recommend the drug Ocrelizumab for her if it became available. My daughter has seven year old twins and runs her own business. It is becoming increasingly more difficult for her to even get out of her house. She fears that it is only a matter of time before she has to give up her business and then rely on state benefits and more costly treatment from the NHS. Surely it would be more cost effective to make available a drug which could reduce her disability and hopefully hold off further decline or the development of SPMS. Ocrelizumab is the first and only hope she could be given of a reduction in her disability.	
56	Public	Patient 5	I was diagnosed with Relapsing Remitting MS in September 2011. I started the clinical trials for Ocrelizumab in January 2012.Having completed the 96 weeks of treatment I started the open label extension. I am currently still receiving Ocrelizumab, during the time that I have been receiving the treatment I haven't had a relapse. I do suffer with the usual symptoms MS - fatigue, unsteady walking, but my life style hasn't really changed, just slowed a bit, I am still able to work full time. I don't know how my life would be affected if Ocrelizumab wasn't available.	Thank you for your comment.
57	Public	NHS professional 1	My key points are: I don’t agree with your judgement that this not a novel treatment. I don’t agree with your comments about the safety profile being “broadly similar to other MS DMTs”. The safety profile is very different to other high potency MS treatments. I don’t feel that patient perspectives have been adequately heard. I hope you will reconsider your decision. Please let me know if you would like fuller details	Thank you for your comment.

Document processed	Organisation name – Stakeholder or respondent	Disclosure on tobacco funding / links	Number of comments extracted	Comments
20180425_ID937 ACD stakeholder comments form_NOVARTIS_FINAL [No ACIC].doc	Novartis Pharmaceuticals UK Limited	none	2	
ACD comments ocrelizumab ID937 MS Trust FINAL [No ACIC].doc	[Multiple Sclerosis Trust]	[None]	10	
ID937 ACD Roche response [CIC].docx	Roche Products Ltd; hereinafter “Roche”	N/A	7	
ID937 ocrelizumab ACD comments David Hunt 25042018.doc	Dr David Hunt, Hon Consultant Neurologist, Anne Rowling Clinic University of Edinburgh Nominated by the MS Society	None.	5	
ID937 Ocrelizumab ACD Sanofi comments form [No ACIC].doc	[Sanofi Genzyme]	[None]	6	
ID937 ocrleizumab ACD comments Helen Ford 10042017AS [no ACIC].doc	Clinical Expert	Nil	4	
MS Society - ACD stakeholder comments [No ACIC].doc	MS Society	None.	6	

Ocrelizumab for treating relapsing multiple sclerosis [ID937]

NICE National Institute for Health and Care Excellence

Consultation on the appraisal consultation document – deadline for comments 17.00 on 25 April 2018 email: TACommB@nice.org.uk / or upload to NICE DOCS

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

Comment number	Comments

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	Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Summary	Roche appreciates the opportunity to provide comments on the NICE Appraisal Consultation Document (ACD) for 'Ocrelizumab for treating relapsing multiple sclerosis [ID937]'. While disappointed that the Committee was unable to recommend ocrelizumab in the ACD, Roche is committed to clarifying the remaining uncertainties to ensure ocrelizumab becomes available to NHS patients. Roche have also submitted a revised Patient Access Scheme for ocrelizumab to support committee decision making in determining ocrelizumab to be a cost-effective treatment option within its marketing authorisation. Roche have submitted an appendix with a revised base case in line with the committee's preferred assumptions: • used mixed treatment comparison estimates for confirmed disability progression at 6 months, with missing data imputed based on 3-month data (see details below and in the Roche ACD response Appendix) • included the potential risk of progressive multifocal leukoencephalopathy (PML) for ocrelizumab (using data from rituximab in rheumatoid arthritis as proxy, see details below) • provided cost-effectiveness estimates for each beta interferon and glatiramer acetate compared with ocrelizumab • used UK MS Survey as the source of EDSS costs • used treatment stopping rates for ocrelizumab and all comparators from the mixed treatment comparison in the absence of evidence for a treatment waning effect (same as in previous base case) However, Roche believe that several conclusions in the ACD are not a reasonable and equitable interpretation of the evidence and encourage the Committee to reconsider its conclusions. The responses below address these themes in turn: • disability progression • subgroups • safety profile • innovation • individual comparisons to beta-interferons and glatiramer acetate • waning of treatment effect
1	**Disability progression** The ACD states in 3.9 that *'the committee concluded that it was uncertain whether ocrelizumab slowed disability progression in the whole relapsing–remitting multiple sclerosis population compared with other treatments because there were differences in the effect size between confirmed disability progression at 3 months and 6 months.'* It also states in 3.11 that *'It would*

be appropriate to use a mixed treatment network to jointly model the outcomes for continued disease progression at 3 months and 6 months.'

Evidence from the OPERA trials confirms that ocrelizumab is a superior treatment to IFNB-1a (Rebif), with high and consistent efficacy in delaying confirmed disability progression (CDP). The direct evidence is clear:

- ocrelizumab is the only disease modifying therapy (DMT) that consistently demonstrated statistically significant reduction in confirmed disability progression as expressed by both CDP-12 and CDP-24 outcomes across two phase 3 studies versus IFNB-1a (Rebif) (see Table 23 of submission document B).
- The effect sizes of ocrelizumab compared with IFNB-1a (Rebif) for CDP-12 and CDP-24 are similar and demonstrate direct evidence of clinical benefit on disability progression.
- Further post hoc analyses of disability progression in the OPERA studies that extends the confirmatory period to 36 and 48 weeks (see Table 1 in Roche ACD response Appendix) demonstrates that ocrelizumab significantly reduces the risk of disability progression compared with IFNB-1a (Rebif) regardless of length of confirmatory period, and that there appears to be a trend for increasing effect sizes with longer confirmatory periods. CDP-36 and CDP-48 are not reported for other comparators hence an indirect treatment comparison could not be implemented in the economic analysis. However, the directional effect could be expected to result in more favourable incremental cost-effectiveness ratios (ICERs) for ocrelizumab.
- The committee concluded that beta-interferons and glatiramer acetate could be considered similar in terms of effectiveness (ACD page 6), hence the results of ocrelizumab versus IFNB-1a (Rebif) in the OPERA studies could be considered generalizable to all beta-interferons and glatiramer acetate.

A mixed treatment comparison (MTC) is required to compare ocrelizumab with DMTs other than IFNB-1a (Rebif). As stated in the submission, the MTCs for CDP-12 were considered more robust than those for CDP-24 due to the better quality and quantity of data informing the CDP-12 network of evidence. The credible intervals for the CDP-24 MTCs were also wider due to added uncertainty which complicates drawing of conclusions. Although we agree with the committee that longer confirmation periods are generally better measures of sustained progression, the precision in the effect size and quality of indirect comparisons is also a function of the size and quality of the trials and available evidence.

To bridge the difference in effect sizes observed in the CDP-12 and CDP-24 MTCs, the committee preferred to see joint modelling of CDP-12 and CDP-24, with missing CDP-24 data imputed based on CDP-12 data.
Thus, Roche have conducted additional analyses using two different methods:

- Model 1: CDP-24 analysis which uses CDP-12 input from any trial that did not report CDP-24 input (see Figure 1 in Roche ACD response Appendix). This method, which

	leads to one CDP output per treatment, was used in the most recent Cochrane review in RRMS [1] and by the Institute for Clinical and Economic Review (ICER) in their MS report published in 2017 [2]. • Model 2: a multivariate model allowing for the relative effects between non-placebo interventions to be exchangeable across outcomes, i.e. by allowing for inference to be made on both measures for comparisons where only one measure is available. This model, adapted from a model developed by Achana and colleagues [3], estimates two CDP effects, one for CDP-12 and one for CDP-24, which are strongly related given the assumptions made by the modelling approach. The results of the new MTC Model 1 suggest that ocrelizumab is more effective than placebo and five of the comparator treatments relevant to the NICE scope – IFNB-1a (Avonex), IFNB-1a (Rebif), IFNB-1b (Betaferon), glatiramer acetate, and teriflunomide (see Figure 2 in the Roche ACD response Appendix). There is no evidence of a statistical difference between ocrelizumab and dimethyl fumarate, fingolimod, natalizumab, alemtuzumab, and pegIFNB-1a as the credible intervals cross 1. The hazard ratios for ocrelizumab versus other comparators in MTC Model 1 typically fall (by point estimate) somewhere between the original CDP-12 and CDP-24 MTCs (see Figure 3 in the Roche ACD response Appendix). The credible intervals are noticeably narrower for new MTC Model 1 than for the original CDP-24 MTC. The results of the new MTC Model 2 suggest that ocrelizumab is more effective than placebo and seven of the comparator treatment relevant to the NICE scope – IFNB-1a (Avonex), IFNB-1a (Rebif), IFNB-1b (Betaferon), glatiramer acetate, teriflunomide, dimethyl fumarate, and fingolimod (see Figure 4 in Roche ACD response Appendix). There is no evidence of a statistical difference between ocrelizumab and natalizumab, alemtuzumab, and pegIFNB-1a as the credible intervals cross 1. The point estimates for ocrelizumab versus comparators were typically improved and the credible intervals were noticeably narrower for the new MTC Model 2 than for the original CDP-24 MTC. The revised base case economic analysis uses the new MTC Model 1, as this was considered more credible as it has been used by reputable institutions like Cochrane and ICER, and is also more conservative than the complex Model 2 method which is presented as scenario analysis only in the Roche ACD response Appendix. These results - both from direct evidence with further analysis of CDP-36 and CDP-48 in the OPERA studies and from indirect comparisons using two new MTC methods that jointly model CDP-12 and CDP-24 as requested by the committee - further strengthen the argument that ocrelizumab slows disability progression in the whole RRMS population.
2	**Subgroups**

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	The ACD states in 3.10 that *'the mixed treatment comparison results are highly uncertain in the highly active and rapidly evolving severe subgroups.'* It also states in 3.11 that '*the committee was aware that the company had included data for the total relapsing–remitting population in the subgroup population networks because data were not available for the population of interest. The committee would have preferred these studies to have been excluded from the network when missing data could not be jointly modelled.'* Roche agree with the Committee and the ERG that there is considerable uncertainty in the subgroup MTC due to the sparsity of data. This is mainly due to the lack of subgroup data published for IFNB-1a (Rebif), IFNB-1a (Avonex) and placebo, i.e. treatments which connect ocrelizumab to the relevant comparators fingolimod and natalizumab, resulting in a disconnected network. For this reason, Roche proposed to use the ITT network as the basis for decision making. In order to connect the network, Roche have had to resort to using ITT data for these nodes under the assumption that there is no treatment effect modification between treatment and subgroup, as is the case in the OPERA trials. As requested by the committee, joint modelling of CDP-12 and CDP-24 was conducted for the HA and RES subgroups using the new MTC Model 1 approach, consistent with approach taken for ITT analysis (see Roche ACD response Appendix). The subgroup results are associated with wider credible intervals than the ITT results due to smaller sample size in subgroups and sparsity of subgroup data. The results suggest, for this reason, that there is no statistical difference between ocrelizumab and fingolimod and alemtuzumab in the HA subgroup, or between ocrelizumab and natalizumab and alemtuzumab in the RES subgroup. Uncertainty in the subgroup MTCs, attributed to factors other than ocrelizumab's package of evidence from two double-blind, double-dummy RCTs compared to an active and appropriate comparator which shows consistent results in ITT and HA and RES subgroups on all major endpoints, should not detract from making a decision about ocrelizumab within its marketing authorisation.
3	**Safety profile** The ACD states in 3.12 that *'adverse events with ocrelizumab are broadly similar to those with other disease-modifying therapies.'* Roche do not agree with this statement and believe it needs contextualisation. In addition, it appears to be inconsistent with what the Committee concluded in 3.12: '*the adverse events were likely to be less frequent with ocrelizumab than with other similar therapies, including alemtuzumab*.' Roche would argue that the paragraph heading needs to specify that adverse events with ocrelizumab are broadly similar to those with moderate-efficacy therapies, but less frequent and less severe than those associated with other high-efficacy treatments. This is further supported by the distinct lack of monitoring with ocrelizumab as compared with the onerous monitoring burden of other high-efficacy treatments.

	Roche have acknowledged the committee's recommendations to include risk of PML in the model, but would like to highlight this remains a potential, rather than actual, risk. Given that there have been no reported cases of de novo PML causally attributed to ocrelizumab to date*, the model used the PML rate from a cumulative analysis of confirmed PML cases in patients receiving rituximab in rheumatoid arthritis as a proxy. This information was based on both spontaneous reports and clinical trial sources as captured in the manufacturer global company safety and clinical databases indicating 2.56 PML cases per 100,000 patients over a period of 9-years [6]. It should be noted that these cases were typically associated with confounding PML risk factors, including prior and concomitant immunosuppressive therapies, unlikely to be present in MS patients. This cumulative rate was annualised (0.00028%) before application in the model.
4	**Innovation** The ACD states in 3.25 that *'ocrelizumab is not innovative. The committee was aware that this was not the first treatment directed at the B-lymphocyte antigen CD20 for multiple sclerosis. However, it was the first to be licenced for the whole relapsing–remitting multiple sclerosis population. It heard from clinical experts that they considered it to have a better safety profile than some other high-efficacy treatments and therefore people with relapsing-remitting multiple sclerosis would need less frequent monitoring compared with other treatments such as alemtuzumab. It also has a low frequency of infusions, which people with relapsing-remitting multiple sclerosis value. Further, it appears to delay progression to secondary progressive multiple sclerosis. The committee recognised that some benefits relating to improvements in EDSS may not have been adequately captured in the modelling. However, it concluded that there is not enough evidence that ocrelizumab is innovative compared with other recent treatment options.'* Roche are particularly concerned by the notion of ocrelizumab not being considered innovative. Ocrelizumab offers a unique combination of efficacy, safety, tolerability and convenience (via both low frequency of infusions and less frequent monitoring than other treatments). This combination of features is not matched by any other licensed DMT for the treatment of RRMS, as profiles of previous DMTs have demonstrated a trade-off between these factors, such that high-efficacy treatments are typically associated with a less favourable safety profile, dosing or monitoring, and vice versa. As heard in the first Appraisal Committee Meeting, the above points combined can have a significant impact on patients living with RRMS. The committee also recognised that some benefits relating to improvements in EDSS may not have been adequately captured in the modelling. Ocrelizumab is one of the very few DMTs

* As of April 2018, two cases of confirmed PML have been reported in two patients treated with ocrelizumab in the post-marketing setting. Both cases were reported as carry-over PML, meaning that both cases were confounded by prior treatment (natalizumab and fingolimod, respectively) before starting treatment with ocrelizumab. Natalizumab is associated with an increased risk of PML while on treatment and following discontinuation and there have been cases of PML reported with fingolimod in the post-marketing setting. [4. Biogen Idec Ltd. 2016, 5. Novartis Pharmaceuticals UK Ltd. 2015.]

	demonstrating an effect on confirmed disability improvement, and the lack of inclusion of this benefit in the model confirms that the presented revised base case is conservative. Ocrelizumab is the first licensed anti-CD20 therapy in MS and rituximab [which we assume the committee referred to] was only ever studied in a dose-finding phase 2 study in RRMS and is not licensed for the treatment of MS. Ocrelizumab and rituximab differ in their structure (humanized versus chimeric antibody), and as a consequence there are anticipated differences in their immunogenicity, safety, and efficacy profiles [7-9]. Roche conclude that ocrelizumab in the context of other currently licenced and reimbursed high-efficacy options, should be considered an innovative treatment for RRMS and would invite the committee to reconsider its conclusion in the ACD in this regard.
5	**Individual comparison to beta-interferons and glatiramer acetate** The ACD states in 3.4 that '*individual comparisons of ocrelizumab with beta interferons and glatiramer acetate are appropriate. The committee noted that, in the ongoing appraisal of beta interferons and glatiramer acetate for treating multiple sclerosis, it had concluded that the beta interferons and glatiramer acetate could be considered similar in terms of effectiveness but not in terms of cost effectiveness.'* To ease decision making, Roche have presented the revised base case based on the 'Cochrane' MTC for individual comparisons as requested in the appendix. These results demonstrate that ocrelizumab is a cost-effective use of NHS resources. Hereby Roche address the only outlier result that needs further explanation. The CDP-24 MTC results for pegIFN-1a suggest that it is more effective than other beta-interferons or glatiramer acetate, and similarly potent to high-efficacy treatments like natalizumab (see Figure 18 of submission document B). This lacks face validity and is contrary to clinical experience with pegIFNB-1a and clinical consensus about equivalence between beta-interferons and glatiramer acetate (as similarly concluded by the committee). Indeed, the EPAR for pegIFNB-1a comments on the unconventional definition of CDP in the single study informing the pegIFN-1a result in the network, and states that post hoc analysis using the conventional CDP-24 definition resulted in smaller effect sizes (post hoc results were not reported in the EPAR) [10]. As this outlier pegIFNB-1a result unreasonably affects the incremental analysis, Roche have presented the incremental analysis of the revised base case excluding pegIFNB-1a. However, additional analyses including pegIFNB-1a are presented in the Roche ACD response Appendix for transparency. Two new scenario analyses are also presented in the Appendix: 1) using the new MTC Model 2 which resolves some of the discrepancy observed in the pegIFNB-1a CDP-24 data (see Figure 4 in Roche ACD response Appendix), and 2) applying efficacy from trial comparator IFNB-1a (Rebif) to all beta-interferons and glatiramer acetate to reflect the committee's conclusion that

	these treatments are clinically equivalent. The latter scenario only varies the costs of drug, administration, monitoring, and AE management, and applies individual all-cause discontinuation rates from the MTC. This scenario analysis has the advantage of making use of the most robust evidence from two head-to-head studies comparing ocrelizumab with IFNB-1a (Rebif), and is in keeping with the committee's conclusion that beta-interferons and glatiramer acetate have similar effectiveness but not cost effectiveness. Both new scenario analyses indicated broadly similar results as the revised base case, and thereby support the robustness of the new base case.
6	**Waning of treatment effect** The ACD states in 3.19 that *'treatment efficacy is likely to wane over time with ocrelizumab.'* It also states that *'the company was unable to provide the committee with evidence of an association between the presence of antibodies and treatment efficacy. The clinical experts explained that they would expect the efficacy of most treatments for multiple sclerosis to wane over time, either because the immune system develops neutralising antibodies that may prevent the treatment from working, or because the disease worsens.'* By definition, neutralising antibodies neutralise the biological effect of the antigen, therefore it would be anticipated that these would have a negative impact on the potential efficacy of treatment. Indeed, there is a wealth of evidence in the literature correlating the presence of neutralising antibodies with reduced efficacy of other DMTs in MS [11-16]. Therefore, the evidence confirms that neutralising antibodies are associated with treatment waning. As such, the negligible proportion of ocrelizumab patients developing anti-drug antibodies suggests neutralising antibodies cannot be a source of treatment waning for ocrelizumab. Additionally, Roche would like to reiterate the evidence initially presented in the manufacturer's submission supporting the notion that there is a low probability of long-term treatment waning with ocrelizumab: • Reduced immunogenicity of ocrelizumab vs. other biological MS DMTs reducing the probability of long-term waning due to formation of neutralising antibodies • Open label extension data demonstrating durable effects on both clinical and MRI disease activity up to 4 years Roche have maintained in the economic model all-cause discontinuation rates as requested by the committee, however do consider this a conservative assumption as a proxy for treatment waning as patients could withdraw from treatment for various reasons including tolerability. Patients withdrawing from treatment revert back to natural history of disease progression of untreated patients, and no longer accrue a treatment benefit in the economic model.

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Conclusion and updated results	An updated base case is provided in response to this ACD which reflects the committee's preferences, as discussed above. In addition, a number of scenario analyses have been conducted as supportive evidence (as also discussed in earlier sections of this response). Full details can be found in the Roche ACD response Appendix; however, a summary is provided below. Finally, Roche has updated the discount of ocrelizumab, to [redacted] equating to a 300 mL vial price of [redacted] and yearly price of [redacted]. All with-PAS results in the appendix account for this new discount. New base case analysis The updated base case results in a QALY gain of [redacted] and a life-year gain of [redacted] for ocrelizumab. The resulting incremental ICER for ocrelizumab compared with glatiramer acetate is £21,720 based on the new PAS for ocrelizumab. This is based on exclusion of alemtuzumab to allow patient choice and exclusion of peg-IFNB-1a due to widely accepted outlier result. The ICERs for ocrelizumab versus beta-interferons and glatimar acetate range between £12,674 and £21,720. The base case results can be considered conservative because the treatment effect of ocrelizumab on disability improvement and on the longer disability progression outcomes CDP-36 and CDP-48 were not captured in the model. New scenario analyses Additional scenario analyses explored the impact of using the MTC Model 2 method to impute CDP-24, and of applying IFNB-1a (Rebif) efficacy results to all other beta-interferons and glatiramer acetate in line with the committee's conclusion of clinical equivalence between these treatments. In the latter scenario – which is preferable due to its simplicity, transparency, and in line with committee's assumptions – ICERs for ocrelizumab range between £12,674 and £26,283 per QALY versus the beta-interferons and glatiramer acetate, including pegIFNB-1a. The new scenarios resulted in broadly similar results as the revised base case, with ICERs for ocrelizumab versus beta-interferons and glatiramer acetate remaining well under the £30,000 per QALY threshold in all cases, and thereby supporting the robustness of the new base case. Subgroup analyses Subgroup analyses were conducted reflecting the committee's preferences and the revised PAS. When allowing patient choice and excluding alemtuzumab, ocrelizumab dominates fingolimod (based on list price) in the HA subgroup. Compared with natalizumab in the RES subgroup, ocrelizumab is estimated to be marginally less effective and much less costly than natalizumab. The subgroup results indicate that ocrelizumab is also a cost-effective treatment option in the HA and RES subgroups. Whilst the Patient Access Schemes associated with some of the comparator are not known to Roche, we hope the committee are satisfied with the updated analyses to deem ocrelizumab a cost-effective option within its marketing authorisation.

Ocrelizumab for treating relapsing multiple sclerosis [ID937]

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	MS Society
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None.
Name of commentator person completing form:	[redacted]
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Example 1	We are concerned that this recommendation may imply that ……..
1	**Summary** The Committee acknowledge within the appraisal consultation document that ocrelizumab would be welcomed by people with MS who would value a treatment with less frequent dosing and monitoring requirements but concluded that they did not consider it as providing unique benefits compared with other treatment options. The MS Society strongly disagrees with this opinion and asks the Committee to take into full consideration the views and experiences of people with MS that were expressed at the committee meeting and in our previous submission. Ocrelizumab has been shown in clinical trials to be a highly effective treatment for relapsing MS and its 6 monthly infusion and side effect profile would make it the treatment of choice for many people with MS. Since the appraisal consultation document has been published we have been contacted by a number of people who have been advised by their neurologists that ocrelizumab would be better suited to their MS than other available treatments. They are concerned that they will no longer be able to access ocrelizumab and have written to describe why they think they would benefit.
2	**Mode of Delivery** At the committee meeting, the patient experts gave oral evidence stressing that ocreliizumab had substantially improved their quality of life. The 6 monthly infusions have meant they have been free from the side effects and obligations involved with taking a treatment with a more frequent dosing schedule. The patient experts at the committee meeting had previously taken beta interferons to treat their MS and the benefit of not having to take frequent injections was noted by both. More people with MS who are taking ocrelizumab have since written to us expressing what a substantial impact less frequent administration and monitoring has had on their life, one individual commented “No longer having my day to day life run by medication means I'm able to have a normal life. You simply cannot put a price on that by itself.” This comment was from someone who had previously been taking dimethyl fumurate, taking two tablets a day. For people who alternatively would be taking daily tablets ocrelizumab has allowed them to engage in activities which were previously difficult. This includes socialising, holidays and not having to plan daily activities around taking medication. The committee should take into account the improved quality of life which comes with a much less onerous treatment schedule.
3	**Side Effects** The committee acknowledges that adverse events are less likely to be experienced with ocrelizumab than with other MS treatments and that though the risk of PML cannot be ruled out it is ‘likely to be lower than natalizumab’. We have heard from people who are currently taking natalizumab who have been told they are at high risk of contracting PML. They have told us that they would like the opportunity to take ocrelizumab instead and are concerned that they will now not be able to. One person who is on natalizumab explained that she has been waiting for ocrelizumab to be approved for over a year and that while natalizumab is controlling her MS, she feels that she is playing ‘russian roulette’ every time she has an infusion. ‘I had an extreme allergic reaction to Tysabri so was put onto a less effective DMT with the hope that if I relapsed on that, in the future Ocrelizumab would be an option.’ - Person with MS. The clinical experts explained that ocrelizumab would likely be used as a first line therapy option for those who are unable to tolerate the side effects of alemtuzumab and that they considered to have a

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	better safety profile than other high-efficacy treatments. This means there would be a clear place for ocrelizumab within the treatment pathway for relapsing MS. The potential side effects for alemtuzumab range from thyroid and kidney problems to idiopathic thrombocytopenic purpura (ITP) which causes many people concern before starting treatment.
4	**Innovation** The committee concluded that ocrelizumab should not be considered an innovative treatment despite it being the first licensed drug for MS which targets B-cells. We strongly disagree with this conclusion. People with MS react differently to different treatments, the more options available which have different mechanisms will result in more people finding the treatment which works best at tackling their MS.
5	**Treatment Waning** The committee has applied a treatment waning effect to ocrelizumab over time without clear evidence to support this. While they may feel that there is not enough evidence to support the model laid out by the company they in turn cannot provide evidence to support that ocrelizumab treatment effect will wane over time to the degree assumed. The committee say that the company's assertion that there were less anti-drug antibodies in the ocrelizumab group was not backed up by evidence of an association between the presence of antibodies and treatment efficacy. However, they also say that treatment waning is likely due to the immune system developing neutralising antibodies. Without evidence to support this claim, the committee is applying one rule to the company and another to itself.
6	**Costs to NHS** Ocrelizumab is likely to reduce additional costs to the NHS due to the number of people who would choose ocrelizumab over natalizumab. The less frequent administration and less arduous monitoring would mean less additional NHS resources would be required. This should be fully considered when weighing up ocrelizumab's cost effectiveness.

Insert extra rows as needed

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	[**Multiple Sclerosis Trust**]
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[**None**]
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Example 1	We are concerned that this recommendation may imply that ……..
1	The MS Trust is extremely disappointed that ocrelizumab is not recommended for relapsing forms of multiple sclerosis in adults with active disease defined by clinical or imaging features.
2	**Innovative nature of ocrelizumab** In reviewing the innovative nature of ocrelizumab, the committee concludes that there is not enough evidence that ocrelizumab is innovative compared with other treatment options (3.25). **We strongly disagree with this assessment.** To demonstrate the innovative nature of ocrelizumab, we have compared ocrelizumab to disease modifying drugs with a similar degree of effectiveness: natalizumab, fingolimod and alemtuzumab.
3	• **Novel mechanism of action** Ocrelizumab is the first licensed treatment directed at the B-lymphocyte antigen CD20 for MS. It is the first humanized CD20 monoclonal antibody so it is expected to be less immunogenic with repeated infusions. Through a variety of different mechanisms of action, each of the other disease modifying drugs acts via T-lymphocytes. There is increasing research evidence that B-lymphocytes, particularly B memory cells, play a pivotal role in the pathogenesis of MS, so ocrelizumab represents a highly targeted approach to treatment.
4	• **Convenient six monthly dosing schedule** Ocrelizumab offers a novel treatment schedule, aiding adherence, minimising impact on NHS infusion services and reducing the burden of treatment for patients. Both patient and clinical experts emphasised in their written submissions and at the committee meeting the benefits of less frequent hospital visits. Treatment burden: • Ocrelizumab: 2 infusions/year. • Natalizumab: 12 infusions/year. This has a significant impact on NHS infusion services, and for the patient requires frequent visits to hospital, which leads to time away from work or family commitments and often lengthy and costly journeys. The need for monthly treatments can have further practical implications, for example for someone planning extended overseas travel. • Fingolimod: 365 tablets/year. Offers convenience of self-treatment at home, but adherence can be a problem since people often forget to take fingolimod on a regular basis. Problems with home delivery of medication can be very frustrating and time-consuming, adding to the burden of treatment. • Alemtuzumab: two treatment courses, infusions for five consecutive days in year 1, infusions for three consecutive days twelve months later. In addition, patients must avoid exposure to infections, in particular avoid foods that may be a source of Listeria two weeks before, during and one month after treatment. Patients often feel very unwell for some weeks after treatment, needing to take time off work and are unable to carry out family responsibilities. Furthermore, we understand that NHS England is currently refusing to fund a third course of alemtuzumab for people with breakthrough disease. As the five year follow-ups alemtuzumab clinical trials reported that nearly half of the participants received retreatment, the refusal to fund a third course is a significant concern for both clinicians and patients and adds to treatment burden.
5	• **Low risk of side effects**

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	A combination of high efficacy and low level of serious side effects makes ocrelizumab an attractive alternative to other highly effective disease modifying drugs. Side effects: • Ocrelizumab: infusion reactions; respiratory tract infections; herpes infection; hepatitis B reactivation; neutropenia; very low risk of progressive multifocal leukoencephalopathy (PML). • Natalizumab: higher risk of PML - serious, potentially fatal, brain infection caused by reactivation of JC virus, increased risk after 2 years of treatment; infusion reactions; liver problems; severe allergic reaction during infusion • Fingolimod: cardiac problems on first dose; herpes infection; liver enzyme problems; lymphopenia; macular oedema; basal cell carcinoma; opportunistic infections; low risk of PML • Alemtuzumab: infusion reactions; opportunistic infections; thyroid problems; idiopathic thrombocytopenic purpura; kidney problems
6	• **Minimal monitoring requirements** The low level of side effects with ocrelizumab is reflected by minimal requirement for monitoring. This reduces pressure on NHS resources and is very much more convenient for patient. Monitoring burden: • Ocrelizumab: hepatitis B screening before first dose; no requirement for blood or urine tests or other routine monitoring • Natalizumab: annual MRIs; six-monthly blood tests for JC virus while virus levels negative or low • Fingolimod: cardiovascular monitoring with first dose; before first dose check chickenpox status and vaccinate if necessary; regular blood tests; eye test at 3-4 months after starting treatment; annual skin check • Alemtuzumab: monthly blood and urine tests for four years after last treatment course
7	**Cost effectiveness estimates** The committee notes a number of preferred economic analyses (3.21) and we trust that the manufacturer will provide these. We entirely recognise the importance of establishing cost effectiveness for a new treatment, but we feel that the appraisal process continues to be dominated by a very technical analysis of the economic model. This gives little opportunity for stakeholders with limited expertise in health economics to be able to participate and challenge assumptions. There is a danger of the appraisal process being consumed by hypothetical manipulation of the mathematical model and disconnected from the practical reality of clinical practice. This issue is further exacerbated by redaction of data at committee meetings and from the ACD. We understand the confidential nature of patient access schemes, but this makes it impossible for consultees to engage in discussions of cost effectiveness which are absolutely critical to decision making. Although cost effectiveness estimates take account of comparative costs of treatment and monitoring, they do not take account of supply of limited resources. Cost effectiveness estimates do not reflect the real-world impact of resourcing treatment and monitoring in the over-stretched NHS or the impact on people's lives. The lower level of monitoring and treatment required for ocrelizumab offer benefits for both the NHS and patients which cannot be captured by economic models.
8	**Treatment waning** There is no clinical evidence for treatment waning. The manufacturer has been very clear that ocrelizumab causes negligible levels of neutralizing antibody and that 4 year open label extension data shows sustained treatment efficacy.

	Treatment waning was introduced during the fingolimod appraisal (TA254). The manufacturer carried out a sensitivity analysis on their economic model to see what would happen if there was a **hypothetical** treatment waning and, not surprisingly, the ICER increased. The concept of treatment waning is without precedent in previous MS NICE appraisals. Treatment waning is **hypothetical,** was used to test the responsiveness of a mathematical model and was not based on clinical observation. While we acknowledge that it is difficult to extrapolate two year clinical trial data to long term treatment, we wish to emphasise that there is **no clinical evidence to support loss of efficacy**. Moreover, there is no evidence to justify the arbitrary choice of discontinuation rates as a proxy for treatment waning. There are many factors influencing discontinuation rates, from intolerable side effects through differences in mode and frequency of administration to personal difficulties in attending a study centre; presumed treatment waning over a two year clinical trial is going to be one of the least likely reasons for discontinuing treatment. The ACD states (3.19, p15) "Clinical experts explained that they would expect the efficacy of most treatments for multiple sclerosis to wane over time, either because the immune system develops neutralizing antibodies that may prevent the treatment form working, or because the disease worsens". This is a reasonable, professionally cautious response to the Committee's question. However, the company has already noted that ocrelizumab causes negligible levels of neutralising antibodies; disease worsening is implicit in the economic model. The use of treatment waning in multiple sclerosis technology appraisals has become de facto, in the absence of clinical evidence or biological plausibility, the only purpose being to force an increase in the ICER. Unless this is a routine assumption for all drug technology appraisals, we consider this to be inequitable treatment for MS drugs and completely unjustified.
9	**Patient experience** **We do not feel that the advantages of ocrelizumab for people with MS have been adequately stated or taken into account in the ACD.** The appraisal consultation document does not reflect the very positive experience of patient experts expressed at the committee meeting and in submissions from patient organisations. At the committee meeting, a member of the committee directly asked the patient experts about their experience of ocrelizumab. One of the patient experts described how she was initially taking Rebif but found the flu-like side effects debilitating. On switching to ocrelizumab, she found the six-monthly treatment schedule much less burdensome, and experienced improvements in function and cognition. In her own words: "I didn't realise how ill I was until I wasn't ill." The second patient expert stated that ocrelizumab had genuinely worked for her, she now leads a very normal life and doesn't consider herself to be disabled in any way.
10	**Conclusion** It is our view that ocrelizumab offers a unique combination of novel mechanism of action, convenient dosing schedule, low risk of side effects and minimal monitoring. This combination sets it apart from other disease modifying drugs and makes it a valuable additional treatment for people with relapsing remitting MS and for the NHS. Despite the overall effectiveness of disease modifying drugs for reducing frequency and severity of MS relapses, any one of them can simply fail to work in a particular patient, or cause debilitating side effects. Clinicians lack tools to predict who would respond well to a specific therapy. A wider range of therapies gives greater scope for personalised treatment. Research evidence demonstrates the importance of active, early treatment of relapsing remitting MS

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	to prevent axonal damage and avoid irreversible disability. The EMA has licensed ocrelizumab because it is a highly effective, safe drug for people with relapsing MS. The difficulty in calculating cost effectiveness of MS drugs is well recognised, particularly as the trial data does not address the long-term benefits of treatment. People with MS in the UK are at risk of lagging even further behind other developed countries in their access to licensed drugs. The MS Trust encourages the Committee to recognise that ocrelizumab would be an important addition to the disease modifying drugs approved for relapsing remitting MS. As with other disease modifying therapies, ocrelizumab should be prescribed by neurologists, with commencement of therapy and ongoing monitoring provided by specialist MS nurses.

Insert extra rows as needed

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Association of British Neurologists
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[**Insert disclosure here**]
Name of commentator person completing form:	[redacted]

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Example 1	We are concerned that this recommendation may imply that ……..
1	Commenting on behalf of the Association Of British Neurologist Advisory Group on Neuro-inflammation, I must express our disappointment at the rejection of the use of Ocrelizumab for Relapsing remitting multiple sclerosis. We believe it has the advantages of a unique mechanism of action among licensed drugs.It is one of the most highly effective at reducing relapses, reducing active lesions on MRI and on disability progression . It has a better overall safety profile than other highly active drugs. The risk of PML being much less than with Natalizumab. The risk of auto immune disease is much less than Alemtuzumab. The practicality of 6 monthly infusion versus every 28 days, while maintaining the ability to stop infusions if there is a medical need or patient falls pregnant is valuable. It will also be less costly. It does not require the 48 month blood and urine tests needed following a course of Alemtuzumab. As it is more specific to B cells it is not so generally immunosupressant as Cladribine.
2	The committee was concerned that the risk of PML might be similar to that of Natalizumab. However the widely used anti CD20 antibody- Ritixumab is a more legitimate comparator. Clifford et al Arch Neurol 68(9) 1156-1164 form 2011 reported only 4 cases in 129,000 people treated of Rheumatoid arthritis, estimating a risk of 1 in 25,000. Whereas for Nataizumab the risk rises as high as 1 in 100 in JCV positive patients treated for several years. Although there has been one case of PML in someone with Ocrelizumab following on from Natalizumab and one now reported following on from fingolimod there have been none so far in those solely treated with ocrelizumb for their MS
3	The committee might also consider the excellent retention and efficacy of off licence use of Ritizumab. The Swedish registry data suggests the 24% of 494 people with relapsing MS had both better efficacy and were more likely to remain on treatment than other fist line drugs. Granqvist et al JAMA 75(3) 320-327 2018. In part this will be due to the 6 monthly dose regimen. Ocrelizumab has a 6 monthly infusion regimen, additionally has phase 3 trial data of high efficacy.
4	Highly effective drugs for MS have a greater beneficial effect in aggressive MS as they prevent more disabling relapses and more disability accrual. Although only 3 and 6 month disability progression was considered in the OPERA 1 and OPERA 2 studies a potential effect on the neurodegenerative aspect of MS can be extrapolated form the ORATORIO study in primary progressive MS where as well as 12 week disability progression 24 week disability progression was also superior to placebo.
5	NICE may be aware that the Association of British Neurologists has recently developed a

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	treatment algorithm together with NHS England to guide management of relapsing Multiple sclerosis. This is out for consultation. The potential place of Ocrelizumab in this treatment algorithm is worth consideration.
6	

Insert extra rows as needed

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Ocrelizumab for treating relapsing multiple sclerosis [ID937]

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	[**Sanofi Genzyme**]
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[**None**]
Name of commentator person completing form:	[redacted]

Comment number	Comments Insert each comment in a new row.

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1 Relevant evidence	Sanofi Genzyme (SGZ) believes that all the relevant evidence has been considered, apart from data on the annualised relapse rate (ARR) in the highly active subgroup which was 0.18 for alemtuzumab (Krieger S *et al.* Neurology Apr 2016, 86 (16 Supplement) S51.003).
2 Section 3.21	SGZ agrees with the committee that the preferred assumptions should include efficacy estimates for confirmed disability progression at 6 months (6CDP). Although there may appear to be correlation between CDP-12 and CDP-24 for ocrelizumab, this is based on the two OPERA studies only. The absence of data on other comparators to validate this, the assumption that CDP-12 and CDP-24 are highly correlated could lead to invalid conclusions.
3 Section 3.25	SGZ believes that the statement in section 3.25 of the ACD stating that ocrelizumab 'was the first to be licensed for the whole relapsing-remitting multiple sclerosis (RRMS) to be potentially misleading. Alemtuzumab is licensed for RRMS therefore we request that this statement is removed.
4 Section 3.19	SGZ agree with the committee that the same waning effect is applied to all comparators as in previous submissions.
5 Section 3.12	SGZ acknowledges that patients who receive alemtuzumab may experience autoimmune diseases such as thyroid disorders. These autoimmune diseases are well known and predictable and in the majority of cases mild or moderate. For example thyroid disorders peak at year 3 (Coles 2017 Neurology). Serious events were reported in less than 2.5% each year and most thyroid events were managed with conventional medical therapy. Within the CARE MS studies, patients who developed thyroid events were permitted to receive re-treatment with alemtuzumab and although experience is limited, patients who were re-treated generally did not experience a worsening in severity of thyroid disorders as stated in the alemtuzumab SmPC. We would prefer the wording to say that 'patients having alemtuzumab experience predictable autoimmune diseases which requires monitoring for a finite period (48 months) after stopping treatment'' as per SmPC.
6 Section 3.20	SGZ agree that two additional courses of alemtuzumab should be modelled for cost-effectiveness as per SmPC. The CARE MS extension studies have demonstrated that alemtuzumab has a durable efficacy with the majority of patients, 63%, not requiring a re-treatment with alemtuzumab. The retreatment rates of alemtuzumab have been published with the retreatment rates in year 3, 4 and 5 being 19.3%, 15.8% and 12.5% respectively. These rates have been applied within the cost-effectiveness model. However, the calculation for year 5 onwards is not correct in the model. The annual rate applied after year 5 should be 6%. This is based on patients that have had a 3rd and 4th course in years 5 onwards from the real world follow up of 87 patients by Touhy et al. As it currently is in the economic model retreatment cycles are double counted in years 5 onwards. As per NICE process we have also provided similar comments on the economic model separately.
7 Stakeholder consultation	SGZ would like to highlight that the question 26 raised within the NICE clinical expert statement and published part of the committee papers refers to alemtuzumab being immunosuppressive, which is also raised within the company submission. Research suggests that alemtuzumab exerts it effects in an immunomodulatory manner through the depletion and repopulation of lymphocytes, including: - Alterations in the number, proportions, and properties of some lymphocyte subsets post-treatment. - Increased representation of regulatory T cell subsets. - Increased representation of memory T- and B-lymphocytes. - Transient effects on components of innate immunity (i.e., neutrophils, macrophages, NK cells) Data from Kovarova ENS 2012, show mean B cell values approached baseline and reached the normal range by 3 months after each treatment course. Mean CD4+ T cell counts approached LLN, on average, 24 months after the last treatment course. Mean CD8+ T cell counts reached LLN ~9

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	months after treatment. The reduction in the level of circulating B and T cells and subsequent repopulation, suggests that alemtuzumab does not produce irreversible immunosuppressive effects, and may be the mechanism in which it reduces the potential for relapse, ultimately delaying disease progression. (https://www.medicines.org.uk/emc/product/5409). Additional data to support this immunomodulatory effect can be found in the following references, Coles Lancet 2012, Hartung 2012 and Kasper 2013. The CARE MS extension studies also indicate a low incidence of infections and serious infections further supporting the lack of an immunosuppressive effect. We ask NICE to consider this when preparing any future ACD/FAD for DMTs within MS.

Insert extra rows as needed

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Pro-forma Response
Executable Model
Ocrelizumab for treating relapsing multiple sclerosis [ID937]

Sanofi Genzyme comments on model

Issue 1

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
Retreatment rates applied in the model for alemtuzumab post 5 years	SGZ agree that two additional courses of alemtuzumab should be modelled for cost-effectiveness as per SmPC. The CARE MS extension studies have demonstrated that alemtuzumab has a durable efficacy with the majority of patients, 63%, not requiring a re-treatment with alemtuzumab. The retreatment rates of alemtuzumab have been published with the retreatment rates in year 3, 4 and 5 being 19.3%, 15.8% and 12.5% respectively. These rates have been applied within the cost-effectiveness model. However, the calculation for year 5 onwards is not correct in the model. The annual rate applied after year 5 should be 6%. This is based on patients that have had a 3rd and 4th course in years 5 onwards from the real world follow up of 87 patients by Touhy et al. As it currently is in the economic model retreatment cycles are double counted in years 5 onwards.	Model was not re-run. As alemtuzumab currently dominates at the list price we do not expect this results to change, however it may change if a PAS price is used for ocrelizumab

Ocrelizumab for treating relapsing multiple sclerosis [ID937]

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	**Novartis Pharmaceuticals UK Limited**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	none
Name of commentator person completing form:	[redacted]

Comment number	Comments

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	Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	Paragraph 3.11. Novartis is concerned about the validity of the novel approach to imputation of missing 6-month confirmed disability progression suggested in the ACD. The rationale for the Committee preferring 6-month to 3-month confirmed data is that patients not yet fully recovered from a recent relapse confound the 3-month data. Given that such confounding is expected to be random there is no *a priori* expectation that the ratio of 3:6 month data in any one study would be consistent with that in any other study of the same drug, unless both trials were sufficiently large in sample size so as to dilute the random error. It may be observed that most trials included in the networks are of 1 or 2 year duration and that trials of older drugs may have been powered to detect differences in relapses rather than 6-month confirmed disability progression. This assumption would become even more problematic in the highly active and rapidly evolving severe subgroups.
2	Paragraph 3.12. Sentence beginning "The patient explained that…" It should be added that the patient was speaking about a specific interferon and that this statement is specific to that drug. Each drug has a distinct adverse event profile and this statement is not applicable across all drugs – in particular, this statement does not apply to non-interferon drugs.
3	Paragraph 3.13 onwards. It is not clear from the ACD whether the company approach of applying some clinical effectiveness to the transition from RRMS to SPMS was accepted by the committee or rejected as suggested by the ERG. It is important for transparency of decision making that this is recorded in the ACD.

Insert extra rows as needed

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Clinical Expert
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Nil
Name of commentator person completing form:	Dr Helen Ford
Comment number	**Comments**

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1	I am disappointed that ocrelizumab has not been recommended, within its marketing authorisation, for treating relapsing remitting MS. In my opinion it would be a useful addition to currently available treatment options for RRMS.
2	3.2: I am concerned that the interpretation of the clinical expert evidence was that the majority of patients would currently start treatment with an injectable DMT such as interferon or glatiramer acetate. Many patients start on a 'first line' DMT which includes the oral treatments dimethyl fumarate and teriflunomide. The use of first line injectable treatments has significantly reduced since the approval of the oral first line drugs.
3	3.12: The adverse events with ocrelizumab are not broadly similar to those with other DMTs. In the CARE-MS I (alemtuzumab) 5 year follow up the incidence of autoimmune thyroid events was 40.7% and in CARE-MS II 37.7%. Patients require monthly blood tests for 48 months from their last treatment with alemtuzumab. I'm not aware of any reports of autoimmune conditions following treatment with ocrelizumab. The overall risk of PML in patients with positive JC virus serology following treatment with natalizumab is greater than 4/1000. There have been no reported cases attributed to treatment with ocrelizumab and any risk is likely to be significantly lower than that associated with natalizumab.
4	3.19: The clinical experts advised that patients on treatment with natalizumab can remain relapse free for years and only on stopping treatment eg for pregnancy does the disease re-emerge. This is against the concept of treatment waning. The clinical experts advised of the uncertainty of the role of neutralising antibodies in treatment waning. For anti-CD20 mAbs there has not been a consistent association between immunogenicity and lack of efficacy or adverse effects. For ocrelizumab immunogenicity was limited, with only 0.4%of ocrelizumab-treated patients in the two trials developing anti-drug antibodies.
5	
6	

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Dr David Hunt [redacted] [redacted] [redacted]
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None.
Name of commentator person completing form:	David Hunt

Comment number	Comments

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1	**Summary** I disagree with the conclusion that ocrelizumab does not offer unique benefits compared with other treatment options. People with MS, particularly active forms of MS, have an unmet need for safe, high efficacy treatments. Alemtuzumab and natalizumab are both recognised as high efficacy treatments, and it is recognised that ocrelizumab is a new third high efficacy option. There are people with active MS for whom natalizumab/alemtuzumab are not appropriate or contraindicated. For natalizumab, these are patients with evidence of JC virus infection, who are at long-term risk of PML. For alemtuzumab, these are patients who have other autoimmune diseases, or concerns about developing secondary autoimmunity. These are patient groups for whom ocrelizumab would represent an important alternative high efficacy option.
2	**Mode of Delivery** The mode of delivery of ocrelizumab offers important advantage over many current medications (Alemtuzumab – the large majority of patients have significant cytokine release syndrome reactions requiring careful monitoring. Natalizumab requires monthly infusions. Fingolimod requires intensive first dose monitoring with cardiac surveillance). Feedback from patients in clinic with MS/other autoimmune disease who receive 6-monthly infusions with rituximab (which has a similar dosing schedule to ocrelizumab) is typically positive, with patients finding this treatment regimen minimally intrusive for their daily lives, with no daily pill/injection and less frequent monitoring. This is concordant with the evidence given by patient experts receiving ocrelizumab therapy.
3	**Side Effects** The full side effect profile of ocrelizumab in the postmarketing setting remains to be established, and it is possible that signals including PML may occur in the early postmarketing setting. However, at this early stage it is reasonable to conclude that the level of PML risk will be favourable compared to natalizumab. Indeed, switching to anti-B cell therapies in natalizumab-treated patients at high-risk of PML has become established practice in a number of centres (Alping et al. Annals Neurology 2016 79 (6) 950-958). At the present time the side-effect profile of ocrelizumab appears to be favourable compared to other high efficacy drugs.
4	**Innovation** B-cell targeted therapies represent a novel mechanism of action in multiple sclerosis, compared to other licensed therapies.
5	**Treatment Waning** I disagree with the conclusions regarding treatment waning. I have seen no evidence in the course of the submission – or my own reading – which provides convincing evidence of this phenomenon. Real-world studies of early use of anti-B cell therapies (rituximab use in Swedish MS registry, Granquist et al. JAMA Neurol. 2018 Mar 1;75(3):320-327) are consistent with sustained efficacy of this drug class, and suggest superiority to other DMTs, including high efficacy drugs such as natalizumab. I particularly disagree with the interpretation of my comments regarding neutralising antibodies While neutralising antibodies develop against almost all biologic agents, their role in negating of the

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	effects of treatment are not always clear and should be considered a form of treatment failure. That is, the drug should be changed in those who develop such antibodies. In those patients who do not develop antibodies, I have seen no evidence of treatment waning. While there is consensus that immunotherapies are likely to be maximally efficacious when given early in the clinical course of multiple sclerosis, these comments should not be interpreted to suggest that, in an individual patient, treatment efficacy wanes over time.
6	

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Comments on the ACD Received from the Public through the NICE Website

Name	[redacted]
Role	Patient
Other role	Project Manager
Organisation	
Location	England
Conflict	N/A
Notes	
Comments on individual sections of the ACD:	
General	I have MS and have been treated with alemtuzumab and 2 years after r2 I believe I have not relapsed. i believe that Â£56 000 is good value as it means I do not need monthly infusions for the rest of time, it is also low maintenance for the nhs long term too. Now if the treatment starts to fail and I start relapsing again, would Ocrelizumab not be a good option to fall back and also this could be the same for people currently on tysabri etc.

Name	[redacted]
Role	Patient
Other role	
Organisation	
Location	England
Conflict	No
Notes	
Comments on individual sections of the ACD:	
General	I've read on your website that Nice have initially rejected Ocrelizumab and this terrifies me. After diagnosis in 2015 following 2 relapses is quick succession where I lost pretty much all use in my left side for a couple months had some debilitating spasms and had to take 4 months off work I was put on Tecfidera. The side effects were not great to start with and I continued to relapse and had ongoing issues of fatigue, bladder and bowel problems and balance issues even when not relapsing. I was put on Ocrelizumab in June of last year under a trial and I cannot believe the difference it has made to my life. Firstly, being only every 6 months it is so less invasive on my day to day life. No longer ruled by tablets which made doing anything spontaneous almost impossible as my life had to be planned around taking tablets. Wanna go out for a few unplanned drinks after work? Nope! Have one then have to go home to eat and take tablets. Or constantly have to carry tablets around with you which I can tell you doormen do not like you taking into pubs / clubs. Wanna have a lie in? Nope! Get up and eat so you can take your tablets. No longer having my day to day life run by medication means I'm able to have a normal life. You simply cannot put a price on that by itself. But, on top of all that, my fatigue has almost vanished. I feel

	normal again. My work had improved as I'm no longer struggling to get through the day. I've not soiled myself once, and no longer feel the need to carry around a change of clothes 'just in case'. I've not had any bladder problems, no longer constantly looking for the nearest toilet or having to frequently use public facilities that are dirty. And I'm able to train in a gym. I'm going between 2 and 4 times a week and still have the energy to do things with my family. Before I would be too tired mostly after work to do much. Want a normal sex life? Before we had to pretty much plan it to ensure I had the energy as I used to be falling asleep as soon as I got home. Not now!!! You simply can't put a price on how my life has improved. Yes I still have bad days, I know I'm not cured but they are few and far between rather than being almost every day. But I've not relapsed once and this is the longest I've gone without relapsing since diagnosis. I'm fitter, stronger, healthier, happier, and I have a life. It's given me a NORMAL life where MS isn't the main thing in it. All the things people take for granted life having energy to for the things they want rather than just work and sleep, not carrying spare clothes everywhere. Not having life ruled by daily medication. Making plans, I had stopped making any plans before being on this drug cause most of the time I only ended up cancelling them but not now. I can honestly say I feel this drug has given me my life back. And that is why it really does terrify me that it hasn't been approved. What I am supposed to do after the trial I'm on finishes? Go back to having no normal life? Nice have to see that whilst there may be other drugs that also help slow down progression, it's also about quality of life. Being alive is a lot different to having a life that is wonderful. I cannot stress how much this has given me my life back. Sorry for going on a bit, but I'm honestly scared of having to come off this drug at the end of the trial, as is my husband as he can clearly see the difference in me. I don't want to lose my life again.

Name	[redacted]
Role	Patient
Other role	
Organisation	
Location	England
Conflict	No
Notes	
Comments on individual sections of the ACD:	
General	I was diagnosed with PPMS in 2013 and not given any treatment. In 2015, following a relapse it was decided I was RRMS and put on Tysabri. This worked well for me for 2 years until I was taken off due to rising JC virus levels. Since then I have been on Daclizumab and now Gilenya. My concern is what happens in a few years time when my current treatment stops working?

	I had been pinning my hopes on Ocrelizumab being available by then.

Name	[redacted]
Role	Patient
Other role	
Organisation	
Location	United States
Conflict	
Notes	
Comments on individual sections of the ACD:	
General	Please as a sufferer of MS (SPMS) or Secondary Progressive Multiple Sclerosis I am asking that you do not stop this medication to be avalable via the NHS as it is helpful to people whom are newly diagnosed with MS. Thank you for your time and consideration

Name	[redacted]
Role	Mother of MS patient
Other role	
Organisation	
Location	Scotland
Conflict	No
Notes	
Comments on individual sections of the ACD:	
General	While it is accepted that there are many DMT medications available for RRMS, many of which are fairly effective at reducing the risk of relapse, what they all have in common is that they can only protect against further relapse. Crucially what is different about Ocrelizumab is that is the first drug ever to show reduction in disability. It is the first and only drug to offer this type of hope to anyone with any form of MS. My daughter aged 45 suffers from RRMS. She uses pilates, physiotherapy and diet to hold back the effects of the disease as much as possible. In spite of her commitment and effort she has become much more disabled over the last year. Last year her consultant told her that she would recommend the drug Ocrelizumab for her if it became available. My daughter has seven year old twins and runs her own business. It is becoming increasingly more difficult for her to even get out of her house. She fears that it is only a matter of time before she has to give up her business and then rely on state benefits and more costly treatment from the NHS. Surely it would be more cost effective to make available a drug which could reduce her disability and hopefully hold off further decline or the development of SPMS.

	Ocrelizumab is the first and only hope she could be given of a reduction in her disability.

Name	[redacted]
Role	Patient
Other role	
Organisation	
Location	Wales
Conflict	N/A
Notes	
Comments on individual sections of the ACD:	
General	I was diagnosed with Relapsing Remitting MS in September 2011. I started the clinical trials for Ocrelizumab in January 2012.Having completed the 96 weeks of treatment I started the open label extension. I am currently still receiving Ocrelizumab, during the time that I have been receiving the treatment I haven't had a relapse. I do suffer with the usual symptoms MS - fatigue, unsteady walking, but my life style hasn't really changed, just slowed a bit, I am still able to work full time. I don't know how my life would be affected if Ocrelizumab wasn't available.

Name	[redacted]
Role	NHS Professional
Other role	Consultant Neurologist
Organisation	[redacted]
Location	England
Conflict	
Notes	
Comments on individual sections of the ACD:	
General	My key points are: I don’t agree with your judgement that this not a novel treatment. I don’t agree with your comments about the safety profile being “broadly similar to other MS DMTs”. The safety profile is very different to other high potency MS treatments. I don’t feel that patient perspectives have been adequately heard. I hope you will reconsider your decision. Please let me know if you would like fuller details

Appendix A

This appendix contains the following new evidence and analyses:

- Post hoc disability analysis from the OPERA studies
- New mixed treatment comparisons (MTCs) for CDP-24 with missing data imputed based on CDP-12, as requested by the committee
- New Patient Access Scheme for ocrelizumab
- New base case, as requested by the committee

Post hoc disability analysis from the OPERA studies

Given the committee's preference for longer confirmed disability progression periods, post hoc analyses of disability progression in the OPERA studies was conducted to extend the confirmatory period to 36 and 48 weeks (see Table 1). This analysis demonstrates that ocrelizumab significantly reduces the risk of disability progression compared with IFNB-1a (Rebif) regardless of length of confirmatory period, and that there appears to be a trend for increasing effect sizes with longer confirmatory periods.

CDP-36 and CDP-48 are not reported for other comparators hence an indirect comparison could not be implemented in the economic analysis. However, the directional effect could be expected to result in more favourable ICERs for ocrelizumab.

Table 1 Comparison of disease progression outcomes for ocrelizumab versus IFNB-1a

Disability progression	Pooled analysis (HR, 95% CI, p value)	OPERA I (HR, 95% CI , p value)	OPERA II (HR, 95% CI, p value)
CDP-12	0.60 (0.45, 0.81), 0.0006	0.57 (0.37, 0.90), 0.0139	0.63 (0.42, 0.92), 0.0169
CDP-24	0.60 (0.43, 0.84), 0.0025	0.57 (0.34, 0.95), 0.0278	0.63 (0.40, 0.98), 0.0370
CDP-36	0.50 (0.34, 0.76), 0.0007	0.47 (0.25, 0.87), 0.0143	0.53 (0.31, 0.91), 0.0195
CDP-48	0.43 (0.26, 0.69), 0.0004	0.51 (0.25, 1.03), 0.0558	0.36 (0.19, 0.71), 0.0021

New MTCs for CDP-24 with missing data imputed based on CDP-12 data – ITT analysis

Given the committee's preference for CDP-24 with imputation of missing data based on CDP-12, additional MTCs were conducted by Roche. Two different methods were applied:

- Model 1: CDP-24 analysis which uses CDP-12 input from any trial that did not report CDP-24 input (see Figure 1). This method, which leads to one CDP output per treatment, was used in the most recent Cochrane review in RRMS [1] and by the Institute for Clinical and Economic Review (ICER) in their MS report published in 2017 [2].
- Model 2: a multivariate model allowing for the relative effects between non-placebo interventions to be exchangeable across outcomes, i.e. by allowing for inference to be made on both measures for comparisons where only one measure is available. This model, adapted from a model developed by Achana and colleagues [3], estimates two CDP effects, one for CDP-12 and one for CDP-24, which are strongly related given the assumptions made by the modelling approach.

The results of new MTC Model 1 suggest that ocrelizumab is more effective than placebo and five of the comparator treatments relevant to the NICE scope – IFNB-1a (Avonex), IFNB-1a (Rebif), IFNB-1b (Betaferon), glatiramer acetate, and teriflunomide (see Figure 2). There is no evidence of a statistical difference between ocrelizumab and dimethyl fumarate, fingolimod, natalizumab, alemtuzumab, and pegIFNB-1a as the credible intervals cross 1.

The hazard ratios for ocrelizumab versus other comparators in MTC Model 1 typically fall (by point estimate) somewhere between the original CDP-12 and CDP-24 MTCs (see Figure 3). The credible intervals are noticeably narrower for the new MTC Model 1 than for the original CDP-24 MTC.

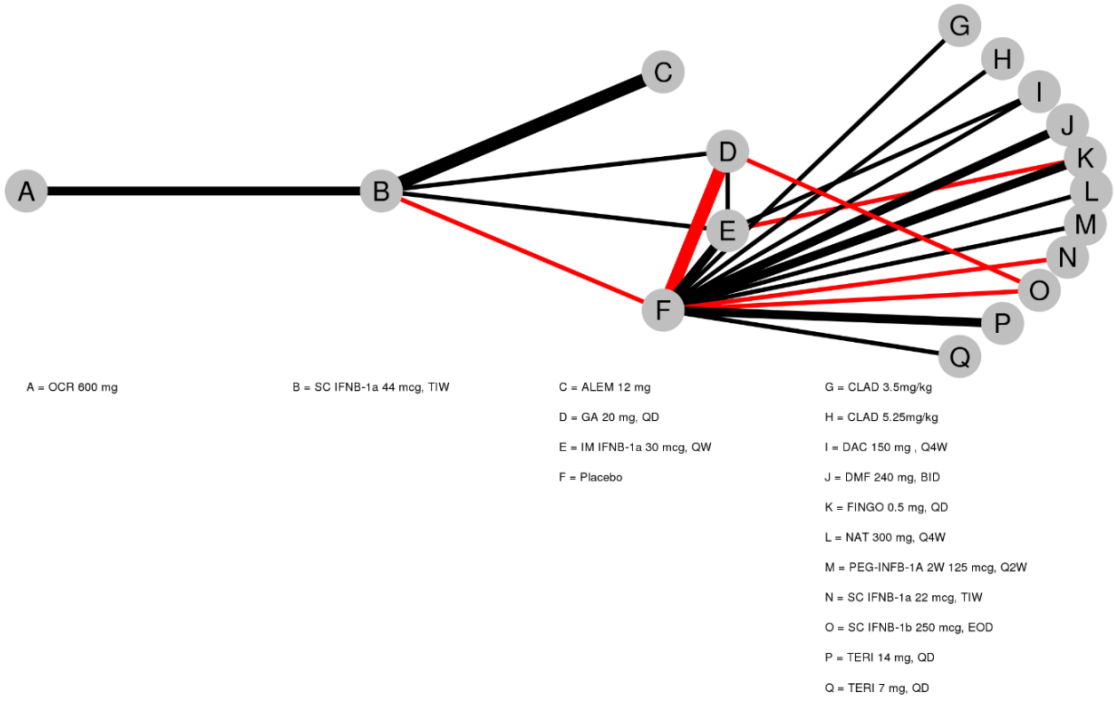
The results of new MTC model 2 suggest that ocrelizumab is more effective than placebo and seven of the comparator treatment relevant to the NICE scope – IFNB-1a (Avonex), IFNB-1a (Rebif), IFNB-1b (Betaferon), glatiramer acetate, teriflunomide, dimethyl fumarate, and fingolimod (see Figure 4). There is no evidence of a statistical difference between ocrelizumab and natalizumab, alemtuzumab, and pegIFNB-1a as the credible intervals cross 1.

The point estimates for ocrelizumab versus comparators were typically improved and the credible intervals were noticeably narrower for the new MTC Model 2 than for the original CDP-24 MTC.

These results - both from direct evidence with further analysis of CDP-36 and CDP-48 in the OPERA studies and from indirect comparisons using two new MTCs that jointly model CDP-12 and CDP-24 as requested by the committee - further strengthen the argument that ocrelizumab slows disability progression in the whole RRMS population.

The revised base case economic analysis uses the new MTC Model 1 as this was considered more credible as it has been used by reputable institutions like Cochrane and ICER, and is also more conservative than the more complex Model 2 method which is presented as scenario analysis only.

Figure 1: Modified Network Diagram for new MTC Model 1 – ITT analysis



Black edges indicate exclusively CDP-24 inputs. Red edges indicate at least 1 CDP-12 input.
Model: RE Inf. (tau~LogNormal A)

Figure 2: Forest plot for new MTC Model 1 – ITT analysis

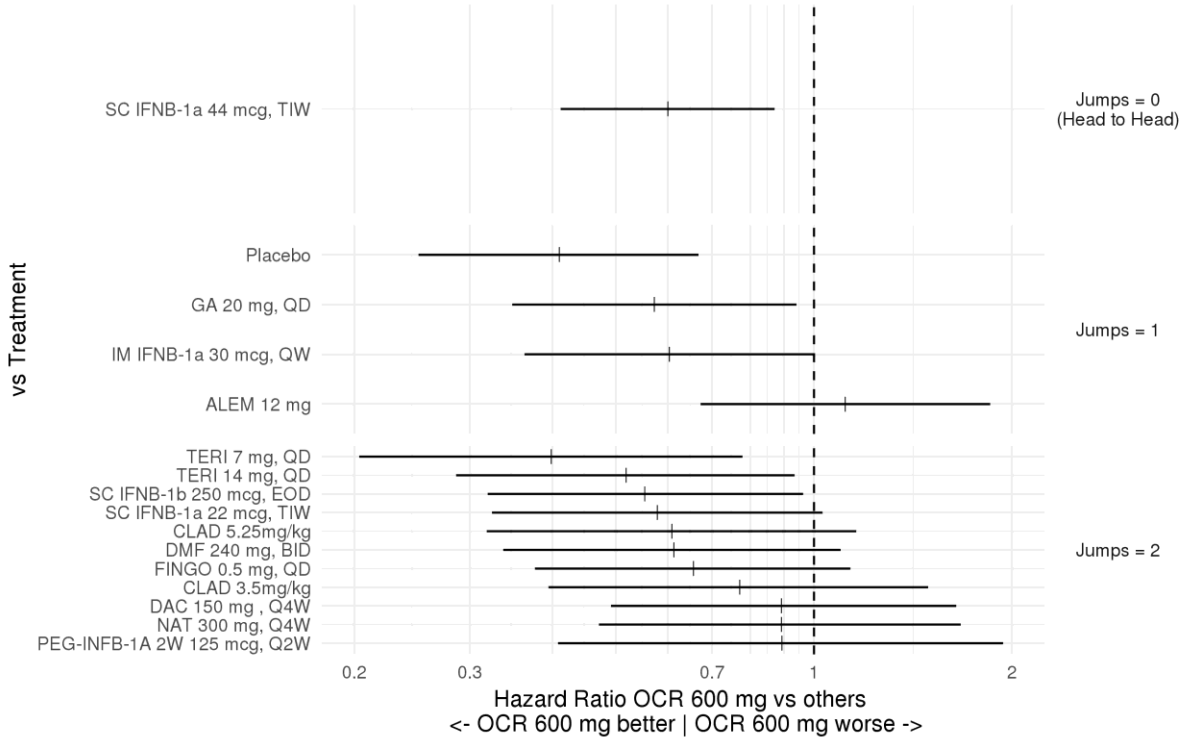


Figure 3: Forest plot comparing MTCs for CDP-12, CDP-24 and Model 1 – ITT analysis

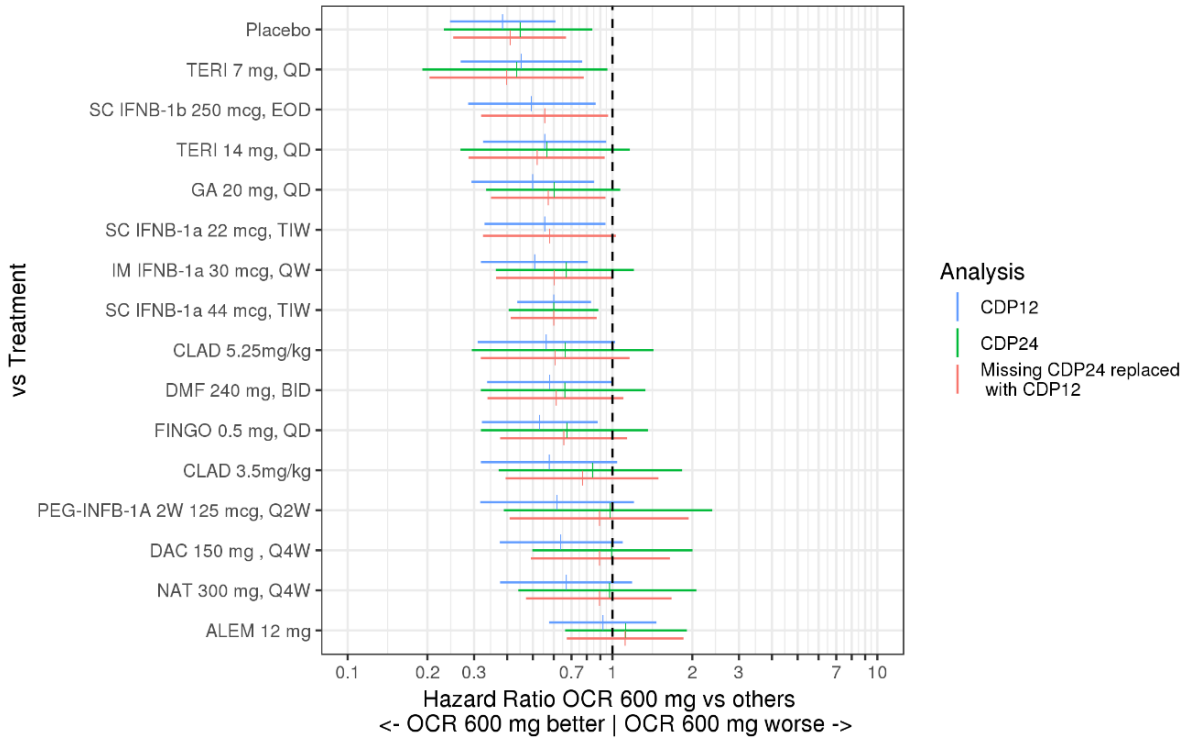
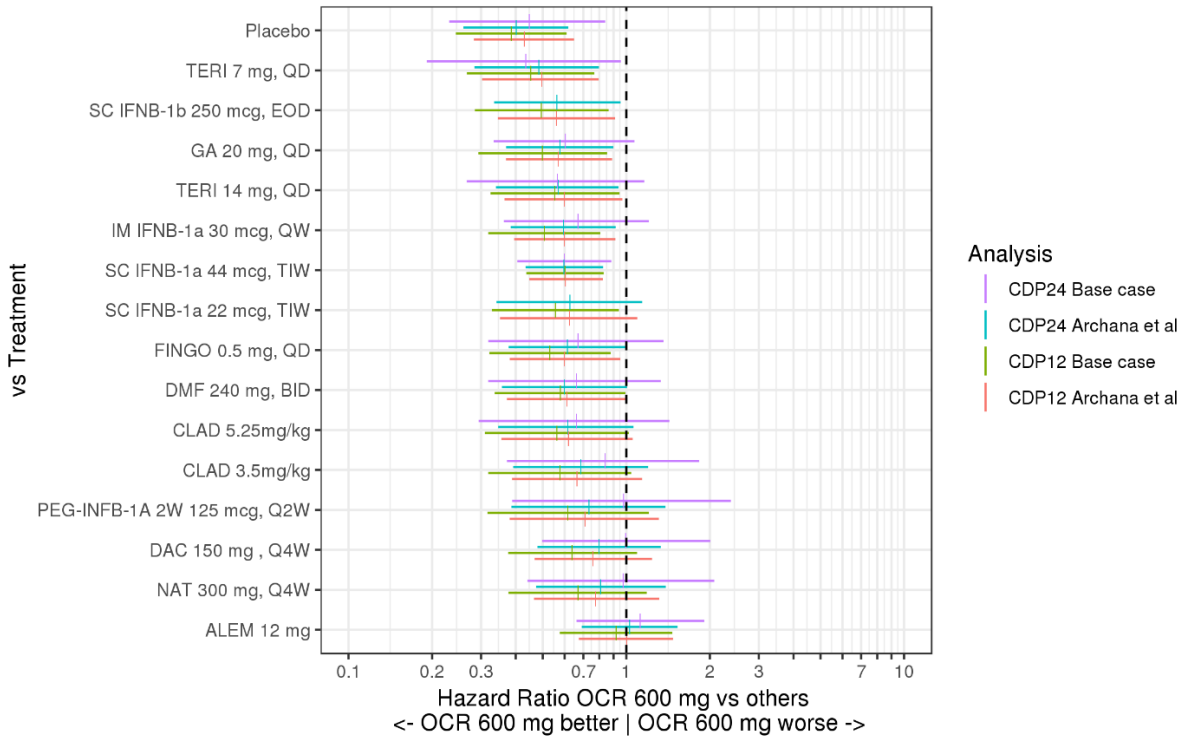


Figure 4: Forest plot comparing MTCs for CDP-12, CDP-24, and Model 2 – ITT analysis



New MTCs for CDP-24 with missing data imputed based on CDP-12 data – subgroup analysis

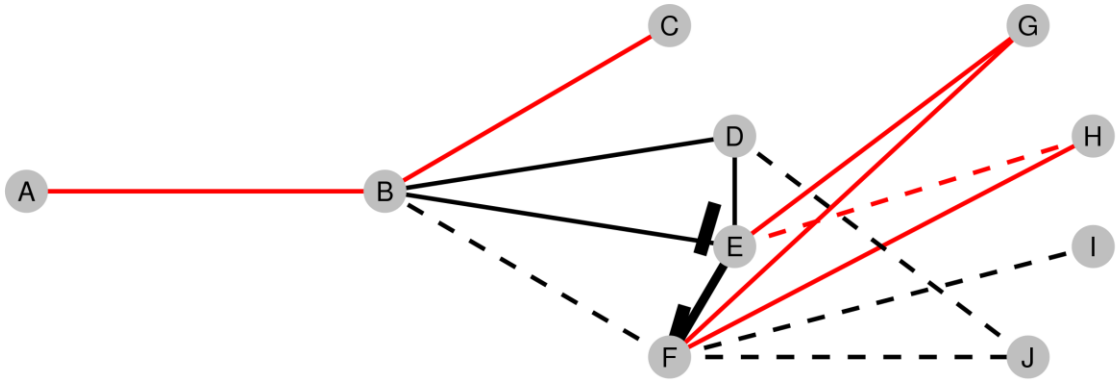
As requested by the committee, joint modelling of CDP-12 and CDP-24 was conducted for the HA and RES subgroups using the new MTC Model 1 approach, consistent with the approach taken for ITT analysis. Figure 5 shows the network diagram and Figure 7 and Figure 7 show the forest plots for the HA subgroup. Figure 8 shows the network diagram and Figure 9 and Figure 10 show the forest plots for the RES subgroups.

The subgroup results are associated with wider credible intervals than the ITT results due to smaller sample size in subgroups and sparsity of subgroup data. The results suggest, for this reason, that there is no statistical difference between ocrelizumab and fingolimod and alemtuzumab in the HA subgroup, or between ocrelizumab and natalizumab and alemtuzumab in the RES subgroup.

Uncertainty in the subgroup MTCs, attributed to factors other than ocrelizumab's package of evidence from two double-blind, double-dummy RCTs compared to an active and appropriate comparator which shows consistent results in ITT and HA and RES subgroups

on all major endpoints, should not detract from making a decision about ocrelizumab within its marketing authorisation.

Figure 5 Modified Network Diagram for new MTC Model 1 – HA subgroup analysis



A = OCR 600 mg
B = SC IFNB-1a 44 mcg, TIW
C = ALEM 12 mg
D = GA 20 mg, QD
E = IM IFNB-1a 30 mcg, QW
F = Placebo
G = DAC 150 mg , Q4W
H = FINGO 0.5 mg, QD
I = SC IFNB-1a 22 mcg, TIW
J = SC IFNB-1b 250 mcg, EOD

Red edges indicate subgroup input, black edges indicate ITT input, dashed lines indicate at least 1 CDP-12 input.

Figure 6 Forest plot for new MTC Model 1 – HA subgroup analysis

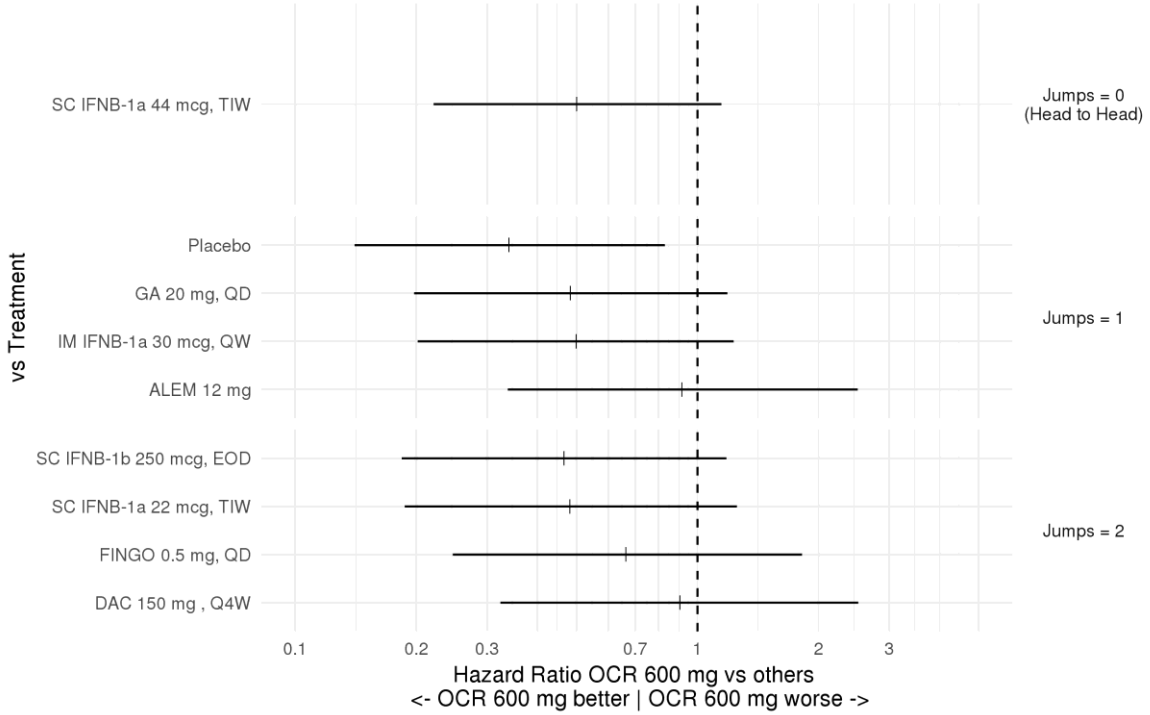


Figure 7 Forest plot comparing MTCs for CDP-12, CDP-24 and Model 1 – HA subgroup analysis

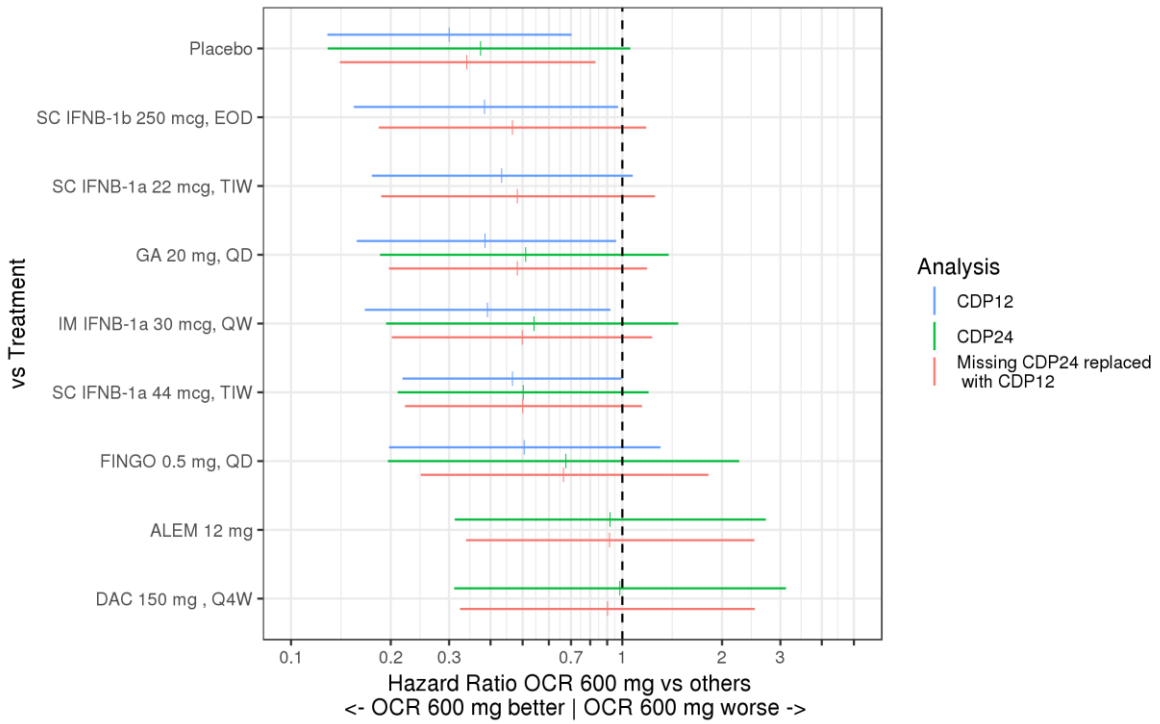
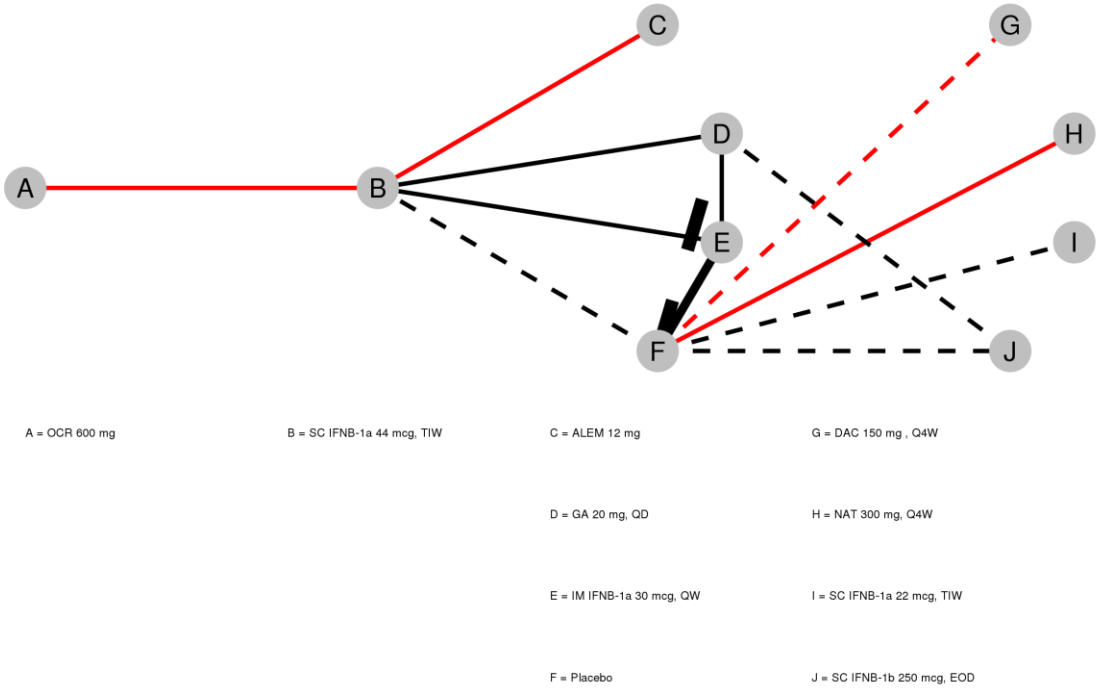


Figure 8 Modified Network Diagram for new MTC Model 1 – RES subgroup analysis



Red edges indicate subgroup input, black edges indicate ITT input, dashed lines indicate at least 1 CDP-12 input.

Figure 9 Forest plot for new MTC Model 1 – RES subgroup analysis

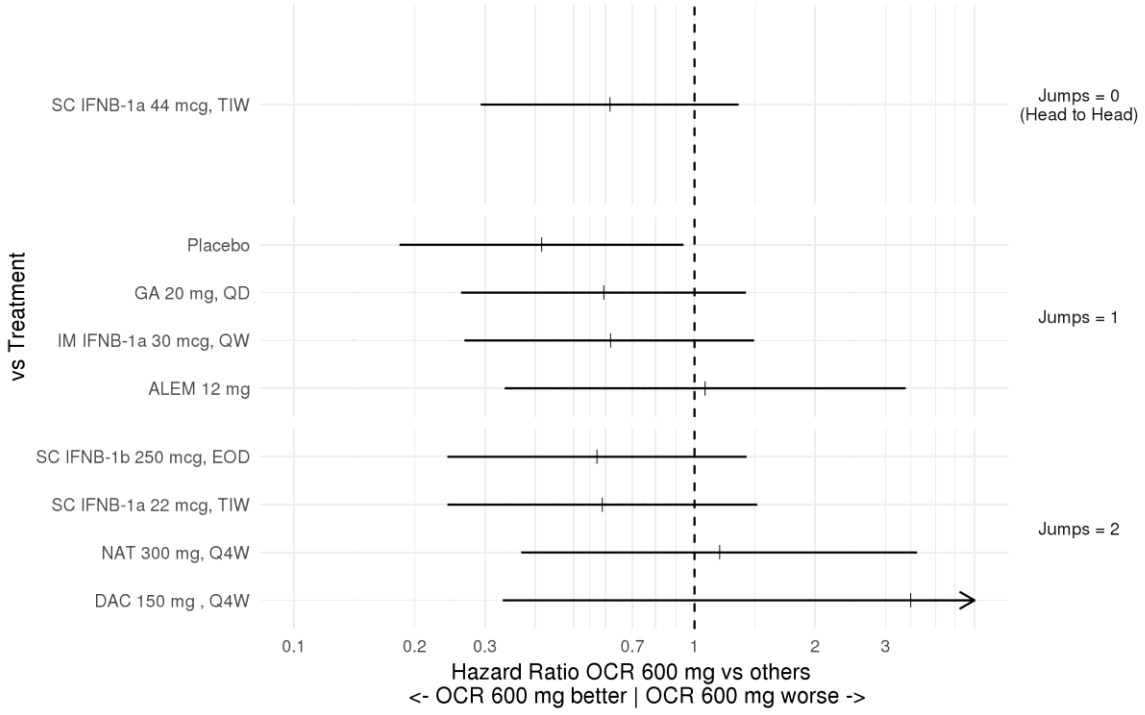
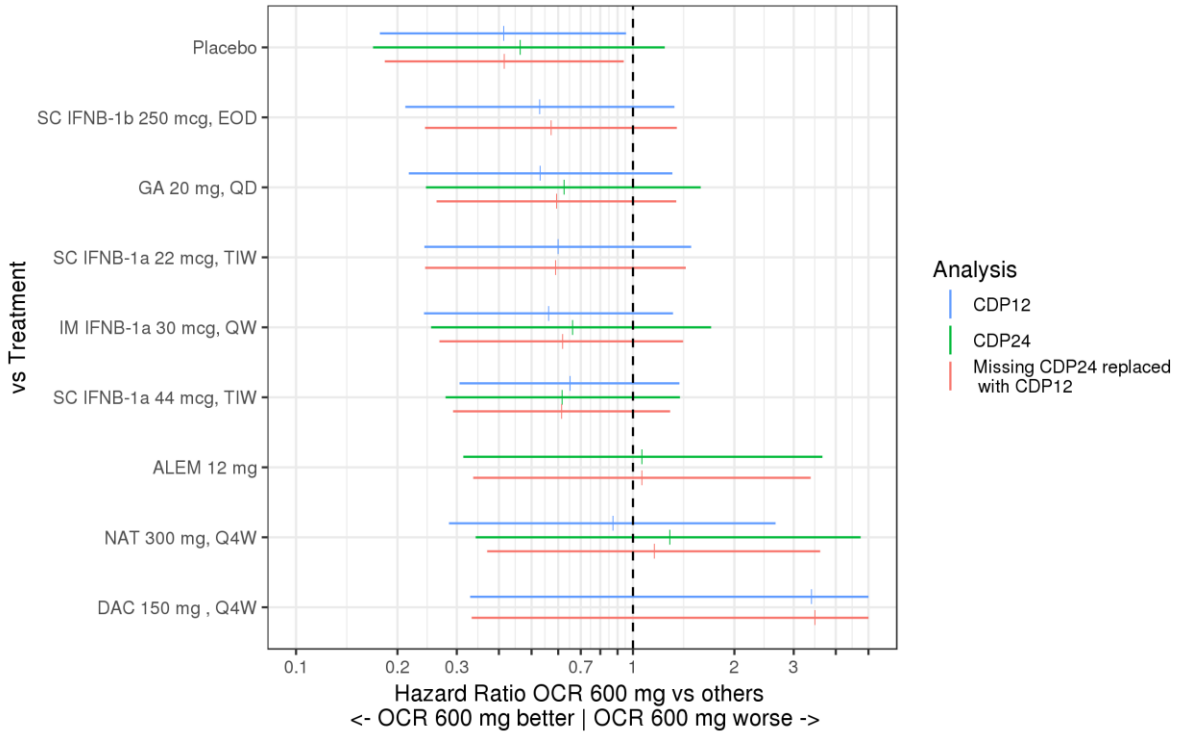


Figure 10 Forest plot comparing MTCs for CDP-12, CDP-24 and Model 1 – RES subgroup analysis



New PAS price

In parallel to the ACD consultation, Roche has submitted an updated PAS proposal to the Department of Health to support committee decision making. The discount has been increased to [redacted], equating to a price per 300 mL vial of [redacted] and yearly cost of [redacted].

Results below incorporate this updated discount.

Results of new base case

The new base case incorporates the following changes which reflect the committee's preferences:

- uses mixed treatment comparison estimates for confirmed disability progression at 6 months, with missing data imputed based on 3-month data (MTC Model 1)

- includes potential risk of PML for ocrelizumab, informed by proxy data from rituximab in rheumatoid arthritis
- provides cost-effectiveness estimates for each beta interferon and glatiramer acetate compared with ocrelizumab
- uses UK MS Survey as the source of EDSS costs (from TA320 inflated to 2015/16)
- uses treatment stopping rates for ocrelizumab and all comparators from the mixed treatment comparison in the absence of evidence for a treatment waning effect (same as in previous base case)

The impact of the above changes of the new base case on the ICER are summarised in Table 2 for the comparison of ocrelizumab with IFNB-1a (Rebif) as a reference. This indicates that including the potential risk of PML has negligible impact on the ICER as the rate is very low. It also indicates that using the UK MS survey as source of EDSS costs has the greatest impact on the ICER, by decreasing it.

The deterministic results of the new base case results are presented in Table 3. This shows that, based on the new PAS for ocrelizumab, the ICERs of ocrelizumab versus the beta-interferons and glatimare acetate range between £11k and £20k, except for the comparison with pegIFNB-1a which is an outlier lacking face validity, as explained in the response to ACD.

The incremental analysis indicates that ocrelizumab is dominated by alemtuzumab (Table 4). However, alemtuzumab is associated with considerable toxicity and monitoring burden, as well was uncertainty over the long-term sustained effect and need for re-treatment. Given that not all patients are able to tolerate alemtuzumab, the incremental analysis was also conducted excluding alemtuzumab (Table 5). The incremental ICER for ocrelizumab compared to glatiramer acetate is £21,720 per QALY. PegIFNB-1a was excluded from the analysis as discussed in the response to ACD. The results including alemtuzumab and pegIFNB-1a are presented in Appendix B for transparency.

Table 2: Impact of committee preferred assumptions on ICER ocrelizumab versus IFNB-1a (Rebif) (based on ocrelizumab new PAS)

Committee preferred assumptions	ICER (£)
Previous base case (based on CDP-12), with ocrelizumab new PAS	*18,255*
• Used MTC estimates for CDP-24, with missing data imputed based on CDP-12 data (new MTC Model 1)	17,870
• Included risk of PML for ocrelizumab	18,255
• Used the UK MS Survey as the source of EDSS costs	13,107
• Used treatment stopping rates for ocrelizumab and all comparators from the mixed treatment comparison in the absence of evidence for a treatment waning effect	18,255
Cumulative impact on ICER	**12,674**

Table 3 Deterministic pairwise analyses, new base case ITT (based on ocrelizumab new PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	ICER ocrelizumab versus comparator (£/QALY)
Ocrelizumab	[redacted]	[redacted]	[redacted]	-
IFNB-1a (Rebif)	[redacted]	[redacted]	[redacted]	12,674
IFNB-1b	[redacted]	[redacted]	[redacted]	16,440
IFNB-1a (Avonex)	[redacted]	[redacted]	[redacted]	18,060
Glatiramer acetate	[redacted]	[redacted]	[redacted]	21,720
PegIFNB-1a	[redacted]	[redacted]	[redacted]	51,668
Teriflunomide	[redacted]	[redacted]	[redacted]	OCR dominant
Dimethyl fumarate	[redacted]	[redacted]	[redacted]	OCR dominant
Alemtuzumab	[redacted]	[redacted]	[redacted]	OCR dominated
Fingolimod*	[redacted]	[redacted]	[redacted]	OCR dominant
Natalizumab*	[redacted]	[redacted]	[redacted]	346,030 SW

Table 4 Incremental analysis, new base case ITT (based on ocrelizumab new PAS, excluding peg-IFNB-1a)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Glatiramer acetate	[redacted]	[redacted]	[redacted]					
IFNB-1a (Avonex)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	331,399	Extendedly dominated
IFNB-1b	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
Alemtuzumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	3,418	3,418
IFNB-1a (Rebif)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	21,720	Dominated
Teriflunomide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
Dimethyl fumarate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	323,136	Dominated
Fingolimod*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	185,163	Dominated
Natalizumab*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	72,534	Dominated

* Outside of NICE scope for this population. ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 5: Incremental analysis, new base case ITT – (based on ocrelizumab new PAS, excluding alemtuzumab and pegIFNB-1a)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Glatiramer acetate	[redacted]	[redacted]	[redacted]					
IFNB-1a (Avonex)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	331,399	Extendedly dominated
IFNB-1b	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
IFNB-1a (Rebif)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	21,720	21,720
Teriflunomide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
Dimethyl fumarate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	323,136	Dominated
Fingolimod*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	185,163	Dominated
Natalizumab*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	72,534	346,030

* Outside of NICE scope for this population. ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Sensitivity analyses

The probabilistic results are broadly similar to the deterministic results, lending support to the overall conclusions.

Alemtuzumab dominates all other DMTs compared to glatiramer acetate in the incremental probabilistic analysis (Table 6). Cost-effectiveness acceptability curves (CEAC) and scatter plots for analyses including alemtuzumab are shown in Appendix B.

When excluding alemtuzumab from the analysis, the probability of ocrelizumab being cost-effective at a £30k ICER threshold is 27.8% based on the new PAS, the highest probability among the DMT options (Figure 11). The probabilistic incremental ICER for ocrelizumab versus glatiramer acetate is £23,985 per QALY.

The cost-effectiveness plane indicates that, compared to ocrelizumab, most other DMTs are situated in the south-west quadrant, meaning they are less efficacious and less costly (Figure 12). The only exceptions are natalizumab which is of broadly similar effectiveness but costlier, and fingolimod which has broadly similar costs but is less effective.

The results of the one-way sensitivity analyses are summarised in a tornado diagram for the comparison of ocrelizumab versus IFNB-1a (Rebif) based on the new ocrelizumab PAS (Figure 13). The results are presented as net monetary benefit for a willingness to pay threshold of £30,000 per QALY. The results were most sensitive to treatment effect on CDP, all other parameters have only modest impact on the results, including administration costs, excess mortality risk, discontinuation, and caregiver disutility.

Scenario analyses generally support the base case results and the cost-effectiveness of ocrelizumab compared to other DMTs does not vary a great deal (Table 8).

Two new scenarios are presented in Table 9:

1) using the new MTC Model 2 for CDP-24 efficacy estimates which resolves some of the discrepancy observed in the pegIFNB-1a CDP-24 data (see Figure 4 and Appendix B for more details), and
2) assuming clinical equivalence between beta-interferons and glatiramer acetate by applying IFNB-1a (Rebif) efficacy (CDP from the new MTC Model 1 and ARR) to all beta-interferons and glatiramer acetate.

The latter scenario only varies the costs of drug, administration, monitoring, and AE management for the different treatments, and applies individual all-cause discontinuation

rates from the MTC. This scenario analysis has the advantage of making use of the most robust evidence from two head-to-head studies comparing ocrelizumab with IFNB-1a (Rebif), and is in keeping with the committee's conclusion that beta-interferons and glatiramer acetate have similar effectiveness but not cost effectiveness.

The range of ICERs for the beta-interferons and glatiramer acetate using the MTC Model 2 are broadly similar to the revised base case (between £13k and £23k per QALY), and the outlier result for pegIFNB-1a is less pronounced using this methodology of CDP-24 imputation. However even with the MTC Model 2 the number of QALYs accrued for pegIFNB-1a is disproportionally high for a beta-interferon.

In the scenario assuming clinical equivalence between the beta-interferons and glatiramer acetate the range of ICERs is also broadly similar to the revised base case (between £13k and £26k per QALY including for ocrelizumab versus pegIFNB-1). This scenario is most appropriate and robust for the committee to consider as it is simple, transparent, in line with the committee's assumptions, and addresses the outlier result of pegIFNB-1a.

Table 6 Probabilistic results, new base case ITT (excluding pegIFNB-1a, based on new ocrelizumab PAS)

Technologies	Mean costs (£)	Mean QALYs	Incremental mean costs	Incremental mean QALYs	Probabilistic ICER versus baseline	Incremental probabilistic ICER
Glatiramer acetate	[redacted]	[redacted]				
IFNB-1b	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
IFNB-1a (Avonex)	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
Alemtuzumab	[redacted]	[redacted]	[redacted]	[redacted]	3,763	3,763
IFNB-1a (Rebif)	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	24,573	Dominated
Teriflunomide	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
Dimethyl fumarate	[redacted]	[redacted]	[redacted]	[redacted]	452,228	Extendedly dominated
Fingolimod*	[redacted]	[redacted]	[redacted]	[redacted]	226,945	Extendedly dominated
Natalizumab*	[redacted]	[redacted]	[redacted]	[redacted]	79,758	Dominated

Table 7 Probabilistic results, new base case ITT (excluding alemtuzumab and pegIFNB-1a, based on new ocrelizumab PAS)

Technologies	Mean costs (£)	Mean QALYs	Incremental mean costs	Incremental mean QALYs	Probabilistic ICER versus baseline	Incremental probabilistic ICER
Glatiramer acetate	[redacted]	[redacted]				
IFNB-1b	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
IFNB-1a (Avonex)	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
IFNB-1a (Rebif)	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	23,985	23,985
Teriflunomide	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
Dimethyl fumarate	[redacted]	[redacted]	[redacted]	[redacted]	503,447	Dominated
Fingolimod*	[redacted]	[redacted]	[redacted]	[redacted]	238,406	Extendedly dominated
Natalizumab*	[redacted]	[redacted]	[redacted]	[redacted]	82,362	417,529

Figure 11 Cost-effectiveness acceptability curve, ITT excluding alemtuzumab (based on new ocrelizumab PAS)

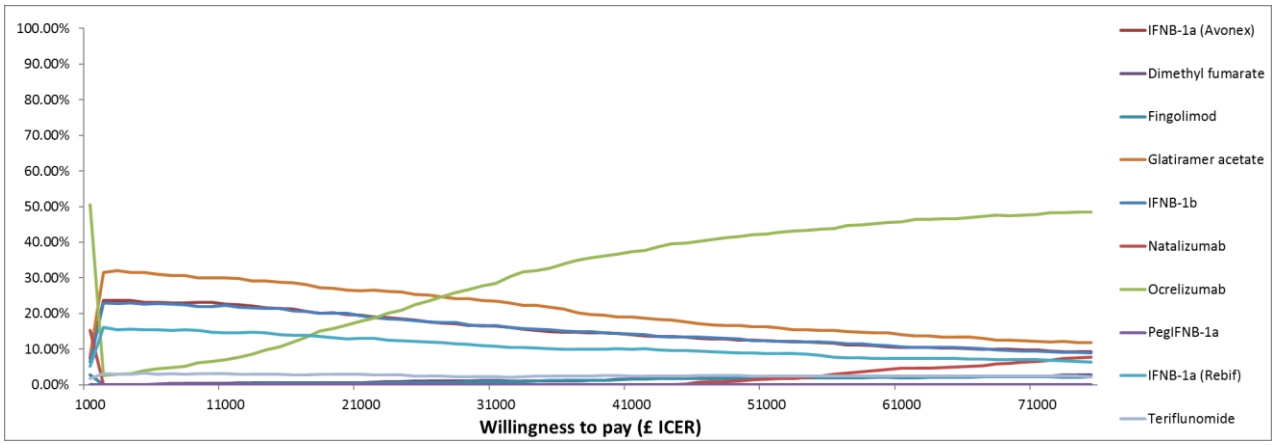


Figure 12 Cost-effectiveness plane for DMTs compared to ocrelizumab, ITT excluding alemtuzumab (based on new ocrelizumab PAS)

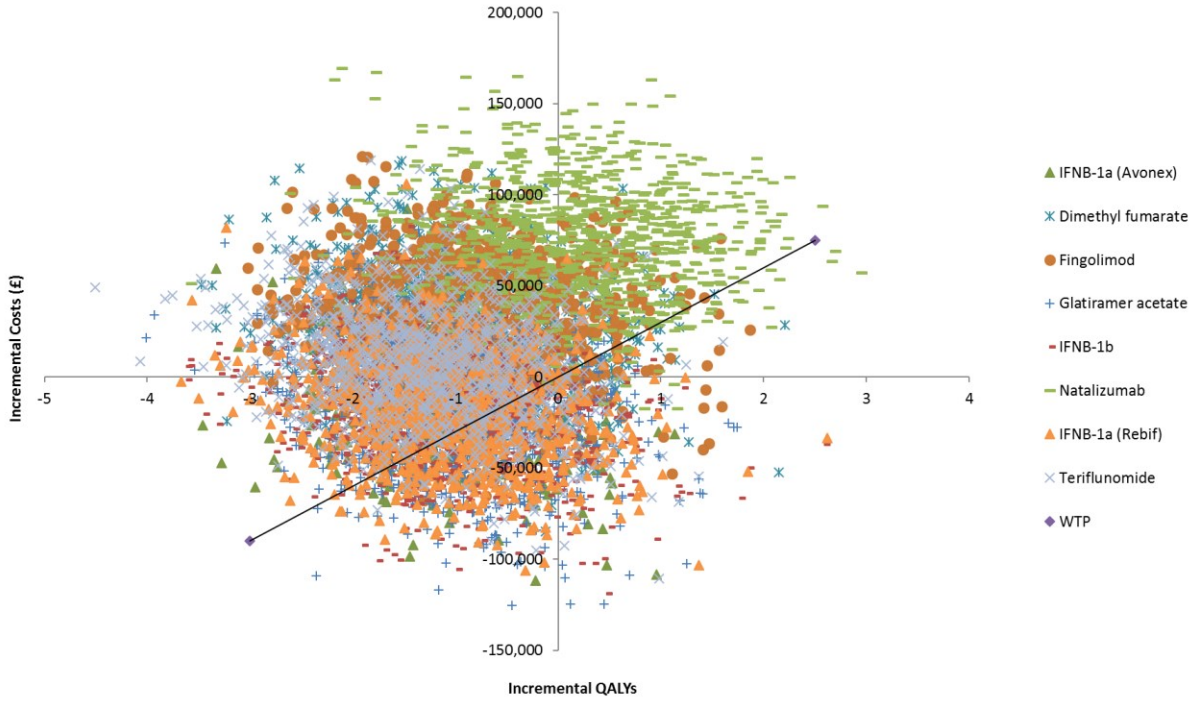


Figure 13: One-way sensitivity analysis for ocrelizumab compared with IFNB-1a (Rebif), new base case with new ocrelizumab PAS

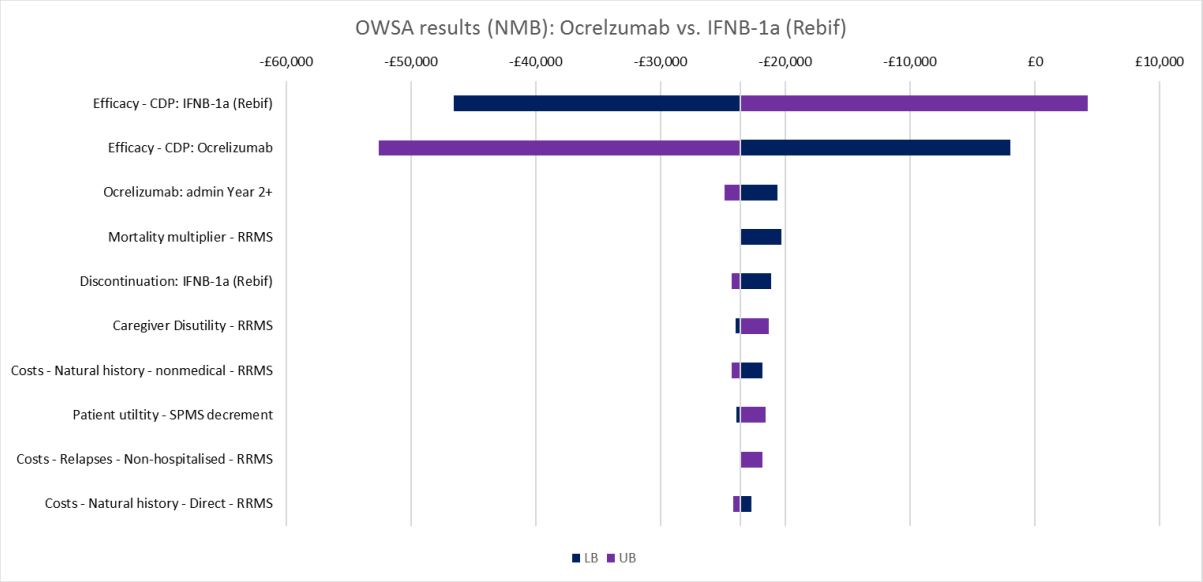


Table 8: Results of scenario analyses, ITT based on ocrelizumab PAS

	ICER ocrelizumab versus comparator									
	Alemtuzumab	IFNB-1a (Avonex)	Dimethyl fumarate	Fingolimod	Glatiramer acetate	IFNB-1b	Natalizumab	peglFNB-1a	IFNB-1 (Rebif)	Teriflunomide
Base case	Dominated	18,060	Ocre Dominant	Ocre Dominant	21,720	16,440	346,030 SW	51,668	12,674	Ocre Dominant
NATURAL HISTORY										
Baseline demographics: UK Risk Sharing Scheme (Pickin et al 2009)	Dominated	16,615	Ocre Dominant	Ocre Dominant	20,089	15,086	422,917 SW	51,642	11,285	Ocre Dominant
Natural history for EDSS transitions in RRMS and SPMS and off treatment: London Ontario	Dominated	17,383	Ocre Dominant	Ocre Dominant	21,585	15,854	491,102 SW	55,468	11,295	Ocre Dominant
ARR natural history: HA subgroup (natalizumab NICE submission)	Dominated	18,064	Ocre Dominant	Ocre Dominant	21,721	16,442	346,065 SW	51,678	12,675	Ocre Dominant
ARR natural history: RES subgroup (natalizumab NICE submission)	Dominated	15,196	Ocre Dominant	Ocre Dominant	19,910	14,689	329,285 SW	46,768	10,811	Ocre Dominant
ARR natural history: Held et al 2005 and UK MS Survey 2005 (alemtuzumab NICE submission)	Dominated	16,319	Ocre Dominant	Ocre Dominant	20,300	15,069	338,440 SW	49,168	11,268	Ocre Dominant
Relapse duration:1 month	Dominated	18,134	Ocre Dominant	Ocre Dominant	21,775	16,482	349,670 SW	51,992	12,708	Ocre Dominant
Relapse duration: 2 months	Dominated	17,988	Ocre Dominant	Ocre Dominant	21,667	16,401	342,604 SW	51,361	12,641	Ocre Dominant
Mortality risk: Kingwell et al 2012	Dominated	16,545	Ocre Dominant	Ocre Dominant	20,415	14,921	395,284 SW	52,304	10,849	Ocre Dominant

EFFICACY										
Efficacy: disability progression set to 12-week confirmation (CDP-12)	Dominated	11,503	Ocre Dominant	Ocre Dominant	15,702	12,219	Ocre Dominant	22,305	13,107	Ocre Dominant
Efficacy: disability progression set to 24-week confirmation (CDP-24)	Dominated	23,439	Ocre Dominant	Ocre Dominant	23,678	27,547	190,581 SW	71,283	11,712	Ocre Dominant
Efficacy: MTC population HA subgroup	NR	11,723	NR	Ocre Dominant	25,249	27,706	NR	NR	7,389	NR
Efficacy: MTC population RES subgroup	NR	21,690	NR	NR	20,089	15,086	76,293 SW	NR	11,678	NR
Treatment waning: 75% after 2 years and 50% after 5 years for all DMTs	Dominated	30,785	Ocre Dominant	Ocre Dominant	35,442	27,037	1,875,337 SW	99,133	22,881	Ocre Dominant
Treatment waning: 75% after 2 years and 50% after 5 years for comparators; 75% after 4 years and 50% after 7 years for ocrelizumab	Dominated	22,857	Ocre Dominant	Ocre Dominant	26,806	20,355	Ocre Dominant	61,601	16,654	Ocre Dominant
All-cause discontinuation: 50% after year 2	Dominated	19,689	Ocre Dominant	Ocre Dominant	23,677	18,678	1,123,918 SW	58,880	13,897	Ocre Dominant
COSTS										
Direct medical costs RRMS and SPMS: Tyas et al. 2007	Dominated	26,807	Ocre Dominant	Ocre Dominant	30,564	25,164	355,548 SW	60,465	21,476	5,123
Direct nonmedical costs RRMS and SPMS: Tyas et al. 2007	Dominated	14,474	Ocre Dominant	Ocre Dominant	18,097	12,869	342,052 SW	48,037	9,068	Ocre Dominant
Relapse cost: average of Hawton et al 2016	Dominated	19,156	Ocre Dominant	Ocre Dominant	22,398	17,112	348,807 SW	53,328	13,400	Ocre Dominant
UTILITIES										
Patient utilities: Orme et al 2007	Dominated	18,889	Ocre Dominant	Ocre Dominant	22,735	17,202	361,189 SW	53,859	13,261	Ocre Dominant

Relapse disutility from OPERA I and II regression analysis	Dominated	17,968	Ocre Dominant	Ocre Dominant	21,652	16,389	341,641 SW	51,275	12,631	Ocre Dominant

Key: NR, not reported; SW = south west quadrant, i.e. less effective and less costly; Dominated, ocrelizumab is dominated by comparator; PAS, patient access scheme

Table 9 Results of new scenario analyses, ITT based on ocrelizumab PAS

	ICER ocrelizumab versus comparator									
	Alemtuzumab	**IFNB-1a (Avonex)**	**Dimethyl fumarate**	**Fingolimod**	**Glatiramer acetate**	**IFNB-1b**	**Natalizumab**	**pegIFNB-1a**	**IFNB-1 (Rebif)**	**Teriflunomide**
Base case	Dominated	18,060	Ocre Dominant	Ocre Dominant	21,720	16,440	346,030 SW	51,668	12,674	Ocre Dominant
EFFICACY										
MTC Model 2 to impute missing CDP-24 data based on CDP-12 data	Dominated	17,126	Ocre Dominant	Ocre Dominant	22,615	18,109	Ocre Dominant	31,673	12,522	Ocre Dominant
IFNB-1a (Rebif) ARR and CDP (from Model 1 MTC) applied to all beta-interferons and glatiramer acetate	Dominated	19,084	Ocre Dominant	Ocre Dominant	26,283	22,737	346,030 SW	20,848	12,674	Ocre Dominant

Subgroup analyses

Subgroup analyses were also conducted reflecting the committee's preferences. The subgroup results indicate that alemtuzumab dominates other treatment options in HA and RES subgroups (**Error! Not a valid bookmark self-reference.** and Table 12). However, excluding alemtuzumab for the above mentioned reasons, ocrelizumab dominates fingolimod (based on list price) in the HA subgroup (Table 11). Compared with natalizumab in the RES subgroup, ocrelizumab was estimated to be marginally less effective and much less costly than natalizumab (Table 13).

The totality of these updated results supports our conclusion that ocrelizumab is cost-effective within its marketing authorisation, including in the HA and RES subgroups.

Table 10 Incremental analysis, new base case HA subgroup (based on MTC Model 1, ocrelizumab new PAS, comparator list price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Alemtuzumab	[redacted]	[redacted]	[redacted]					
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
Fingolimod	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 11 Incremental analysis, new base case HA subgroup (based on MTC Model 1, ocrelizumab new PAS, comparator list price, excluding alemtuzumab)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Ocrelizumab	[redacted]	[redacted]	[redacted]					
Fingolimod	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 12 Incremental analysis, new base case RES subgroup (based on MTC Model 1, ocrelizumab new PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Alemtuzumab	[redacted]	[redacted]	[redacted]					
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
Natalizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	2,091,517	2,091,517

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 13 Incremental analysis, new base case RES subgroup (based on MTC Model 1, ocrelizumab new PAS, excluding alemtuzumab)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Ocrelizumab	[redacted]	[redacted]	[redacted]					
Natalizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	124,078	124,078

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Appendix B

Input and output data of the Model 1 MTC are listed in Table 14 and Table 15 and for the Model 2 MTC in Table 16, Table 17, and Table 18. The JAGS code for the Model 2 MTC is also provided.

Incremental analysis including pegIFNB-1a and alemtuzumab is provided in Table 21.

CEAC and scatter plots for analyses including alemtuzumab are shown in Figure 14 and Figure 15.

Table 14 Input data for MTC Model 1 – ITT analysis

trial_id	endpoint	timepoint	armid	drug	src1_name	src1_value	src2_name	src2_value	loghr	loghrse
ADVANCE	CDP24	48	1	Placebo	NA		NA		0	1
ADVANCE	CDP24	48	2	PEG-INFB-1A 2W 125 mcg, Q2W	di24_orl	0.26	di24_orh	0.81	-0.778897339641131	0.289885871594632
AFFIRM	CDP24	96	1	Placebo	NA		NA		0	1
AFFIRM	CDP24	96	2	NAT 300 mg, Q4W	di24_orl	0.33	di24_orh	0.64	-0.777474863575015	0.168973347421733
BEYOND	CDP12	96	1	SC IFNB-1b 250 mcg, EOD	di12_N	888	di12_per	21	0	1
BEYOND	CDP12	96	2	GA 20 mg, QD	di12_N	445	di12_per	20	-0.0548392672444591	0.12911249842632
Bornstein 1987	CDP12	96	1	Placebo	di12_N	23	di12_n	11	0	1
Bornstein 1987	CDP12	96	2	GA 20 mg, QD	di12_N	25	di12_n	5	-1.07006061026166	0.543132105986777
BRAVO	CDP24	96	1	Placebo	NA		NA		0	1
BRAVO	CDP24	96	2	IM IFNB-1a 30 mcg, QW	di24_orl	0.47	di24_orh	1.14	-0.311997160935814	0.226033379256234
CAMMS223	CDP24	144	1	SC IFNB-1a 44 mcg, TIW	NA		NA		0	1
CAMMS223	CDP24	144	2	ALEM 12 mg	di24_orl	0.11	di24_orh	0.57	-1.38469691567163	0.419682651794944
CARE-MS I	CDP24	96	1	SC IFNB-1a 44 mcg, TIW	NA		NA		0	1
CARE-MS I	CDP24	96	2	ALEM 12 mg	di24_orl	0.4	di24_orh	1.23	-0.354638281244914	0.286557372770021
CARE-MS II	CDP24	96	1	SC IFNB-1a 44 mcg, TIW	NA		NA		0	1
CARE-MS II	CDP24	96	2	ALEM 12 mg	di24_orl	0.38	di24_orh	0.87	-0.553423046797607	0.211306622175561
CLARITY	CDP24	96	1	Placebo	NA		NA		0	1

trial_id	endpoint	timepoint	armid	drug	src1_name	src1_value	src2_name	src2_value	loghr	loghrse
CLARITY	CDP24	96	2	CLAD 3.5mg/kg	di24_orl	0.36	di24_orh	0.79	-0.628686790526526	0.200492069900743
CLARITY	CDP24	96	3	CLAD 5.25mg/kg	di24_orl	0.47	di24_orh	0.97	-0.392740895881371	0.184837596120746
CombiRx	CDP24	144	1	IM IFNB-1a 30 mcg, QW	di24_N	241	di24_n	52	0	1
CombiRx	CDP24	144	2	GA 20 mg, QD	di24_N	246	di24_n	61	0.159137103677619	0.189288964606882
CONFIRM	CDP24	96	1	Placebo	NA		NA		0	1
CONFIRM	CDP24	96	2	GA 20 mg, QD	di24_orl	0.55	di24_orh	1.38	-0.137876750793254	0.234673596919575
CONFIRM	CDP24	96	3	DMF 240 mg, BID	di24_orl	0.37	di24_orh	1.03	-0.482346735551161	0.261176294792197
Copolymer 1 MS trial	CDP12	96	1	Placebo	di12_N	126	di12_per	24.6	0	1
Copolymer 1 MS trial	CDP12	96	2	GA 20 mg, QD	di12_N	125	di12_per	21.6	-0.148707800188344	0.264002496653078
DECIDE	CDP24	144	1	IM IFNB-1a 30 mcg, QW	NA		NA		0	1
DECIDE	CDP24	144	2	DAC 150 mg , Q4W	di24_orl	0.55	di24_orh	0.98	-0.30901985403657	0.147355687101556
DEFINE	CDP24	96	1	Placebo	NA		NA		0	1
DEFINE	CDP24	96	2	DMF 240 mg, BID	di24_orl	0.52	di24_orh	1.14	-0.26144910250013	0.200243553523742
EVIDENCE	CDP24	48	1	IM IFNB-1a 30 mcg, QW	NA		NA		0	1
EVIDENCE	CDP24	48	2	SC IFNB-1a 44 mcg, TIW	di24_orl	0.39	di24_orh	1.25	-0.359232494272118	0.297130635503228
FREEDOMS	CDP24	96	1	Placebo	NA		NA		0	1

trial_id	endpoint	timepoint	armid	drug	src1_name	src1_value	src2_name	src2_value	loghr	loghrse
FREEDOMS	CDP24	96	2	FINGO 0.5 mg, QD	di24_orl	0.44	di24_orh	0.9	-0.463170533863828	0.182556131737756
FREEDOMS II	CDP24	96	1	Placebo	NA		NA		0	1
FREEDOMS II	CDP24	96	2	FINGO 0.5 mg, QD	di24_orl	0.48	di24_orh	1.07	-0.333155263303193	0.204496893763779
IFNB MS	CDP12	240	1	Placebo	di12_N	122	di12_n	56	0	1
IFNB MS	CDP12	240	2	SC IFNB-1b 250 mcg, EOD	di12_N	122	di12_n	43	-0.346226952249605	0.205061099518024
MSCRG	CDP24	96	1	Placebo	di24_N	143	di24_per	34.9	0	1
MSCRG	CDP24	96	2	IM IFNB-1a 30 mcg, QW	di24_N	158	di24_per	21.9	-0.551911996333821	0.222248356590701
OPERA I	CDP24	96	1	SC IFNB-1a 44 mcg, TIW	NA		NA		0	1
OPERA I	CDP24	96	2	OCR 600 mg	di24_orl	0.34	di24_orh	0.95	-0.56505147787974	0.262121522189893
OPERA II	CDP24	96	1	SC IFNB-1a 44 mcg, TIW	NA		NA		0	1
OPERA II	CDP24	96	2	OCR 600 mg	di24_orl	0.4	di24_orh	0.98	-0.468246719595837	0.228593883815468
PRISMS	CDP12	96	1	Placebo	NA		NA		0	1
PRISMS	CDP12	96	2	SC IFNB-1a 22 mcg, TIW	di12_hrl	0.48	di12_hrh	0.98	-0.37708594119886	0.182083282592521
PRISMS	CDP12	96	3	SC IFNB-1a 44 mcg, TIW	di12_hrl	0.43	di12_hrh	0.91	-0.469140374882885	0.191239640516145
REGARD	CDP24	96	1	SC IFNB-1a 44 mcg, TIW	di24_N	386	di24_n	45	0	1
REGARD	CDP24	96	2	GA 20 mg, QD	di24_N	378	di24_n	33	-0.305221867645457	0.22929195146794
SELECT	CDP24	52	1	Placebo	NA		NA		0	1
SELECT	CDP24	52	2	DAC 150 mg , Q4W	di24_orl	0.09	di24_orh	0.63	-1.43499053412422	0.496405650269213

trial_id	endpoint	timepoint	armid	drug	src1_name	src1_value	src2_name	src2_value	loghr	loghrse
TEMSO	CDP24	96	1	Placebo	NA		NA		0	1
TEMSO	CDP24	96	2	TERI 14 mg, QD	di24_orl	0.51	di24_orh	1.11	-0.284492268969761	0.198394022598982
TOWER	CDP24	152	1	Placebo	NA		NA		0	1
TOWER	CDP24	152	2	TERI 7 mg, QD	di24_orl	0.69	di24_orh	1.61	0.0525852488027698	0.216147413364083
TOWER	CDP24	152	3	TERI 14 mg, QD	di24_orl	0.533	di24_orh	1.334	-0.17052595366143	0.234034643446358
TRANSFORMS	CDP12	48	1	IM IFNB-1a 30 mcg, QW	di12_N	429	di12_per	7.9	0	1
TRANSFORMS	CDP12	48	2	FINGO 0.5 mg, QD	di12_N	431	di12_per	5.9	-0.3025238717907	0.262412491215324

Grey annotates CDP-12 data

Table 15 Cross tabulation for MTC Model 1 – ITT analysis (hazard ratios and 95% credible intervals)

	TERI 7 mg, QD	**Placebo**	**TERI 14 mg, QD**	**SC IFNB-1b 250 mcg, EOD**	**GA 20 mg, QD**	**SC IFNB-1a 22 mcg, TIW**	**IM IFNB-1a 30 mcg, QW**	**SC IFNB-1a 44 mcg, TIW**	**CLAD 5.25mg/kg**	**DMF 240 mg, BID**	**FINGO 0.5 mg, QD**	**CLAD 3.5mg/kg**	**NAT 300 mg, Q4W**	**DAC 150 mg , Q4W**	**PEG-INFB-1A 2W 125 mcg, Q2W**	**OCR 600 mg**	**ALEM 12 mg**
TERI 7 mg, QD	**TERI 7 mg, QD**	1.03 (0.66, 1.62)	1.30 (0.80, 2.12)	1.39 (0.80, 2.42)	1.43 (0.86, 2.41)	1.45 (0.79, 2.68)	1.51 (0.91, 2.55)	1.50 (0.87, 2.63)	1.53 (0.82, 2.85)	1.53 (0.87, 2.70)	1.64 (0.97, 2.81)	1.93 (1.02, 3.67)	2.24 (1.22, 4.10)	2.24 (1.24, 4.17)	2.24 (1.05, 4.78)	2.51 (1.28, 4.91)	2.79 (1.47, 5.37)

Placebo	0.97 (0.62, 1.52)	**Placebo**	1.27 (0.90, 1.77)	1.35 (0.99, 1.85)	1.39 (1.10, 1.78)	1.41 (0.94, 2.12)	1.47 (1.15, 1.88)	1.46 (1.07, 2.00)	1.48 (0.97, 2.27)	1.49 (1.06, 2.09)	1.60 (1.21, 2.11)	1.88 (1.19, 2.95)	2.18 (1.46, 3.25)	2.17 (1.47, 3.30)	2.18 (1.19, 3.98)	2.44 (1.50, 3.99)	2.71 (1.72, 4.34)
TERI 14 mg, QD	0.77 (0.47, 1.25)	0.79 (0.57, 1.11)	**TERI 14 g, QD**	1.07 (0.68, 1.69)	1.10 (0.73, 1.67)	1.11 (0.66, 1.89)	1.16 (0.77, 1.76)	1.15 (0.74, 1.84)	1.17 (0.68, 2.01)	1.18 (0.73, 1.89)	1.26 (0.82, 1.95)	1.49 (0.84, 2.60)	1.72 (1.02, 2.90)	1.72 (1.03, 2.94)	1.72 (0.86, 3.45)	1.93 (1.07, 3.50)	2.14 (1.22, 3.83)
SC IFNB-1b 250 mcg, EOD	0.72 (0.41, 1.24)	0.74 (0.54, 1.01)	0.94 (0.59, 1.48)	**SC IFNB-1b 250 mcg, EOD**	1.03 (0.78, 1.37)	1.04 (0.63, 1.73)	1.09 (0.75, 1.56)	1.08 (0.72, 1.63)	1.10 (0.65, 1.85)	1.11 (0.70, 1.71)	1.18 (0.78, 1.78)	1.39 (0.80, 2.39)	1.61 (0.96, 2.67)	1.61 (1.00, 2.64)	1.62 (0.82, 3.19)	1.81 (1.04, 3.13)	2.01 (1.19, 3.43)
GA 20 mg, QD	0.70 (0.41, 1.16)	0.72 (0.56, 0.91)	0.91 (0.60, 1.36)	0.97 (0.73, 1.29)	**GA 20 mg, QD**	1.01 (0.64, 1.59)	1.06 (0.79, 1.39)	1.05 (0.76, 1.45)	1.06 (0.65, 1.72)	1.07 (0.72, 1.57)	1.15 (0.80, 1.63)	1.35 (0.81, 2.23)	1.56 (0.97, 2.48)	1.56 (1.02, 2.42)	1.56 (0.81, 2.99)	1.75 (1.06, 2.88)	1.95 (1.22, 3.13)
SC IFNB-1a 22 mcg, TIW	0.69 (0.37, 1.26)	0.71 (0.47, 1.06)	0.90 (0.53, 1.52)	0.96 (0.58, 1.58)	0.99 (0.63, 1.56)	**SC IFNB-1a 22 mcg, TIW**	1.04 (0.66, 1.65)	1.04 (0.67, 1.61)	1.05 (0.58, 1.89)	1.06 (0.62, 1.78)	1.13 (0.69, 1.84)	1.33 (0.72, 2.43)	1.54 (0.87, 2.71)	1.54 (0.89, 2.74)	1.54 (0.74, 3.20)	1.73 (0.97, 3.09)	1.93 (1.11, 3.38)
IM IFNB-1a 30 mcg, QW	0.66 (0.39, 1.10)	0.68 (0.53, 0.87)	0.86 (0.57, 1.30)	0.92 (0.64, 1.33)	0.95 (0.72, 1.26)	0.96 (0.61, 1.52)	**IM IFNB-1a 30 mcg, QW**	0.99 (0.71, 1.40)	1.01 (0.62, 1.65)	1.01 (0.67, 1.53)	1.09 (0.78, 1.51)	1.28 (0.76, 2.13)	1.48 (0.92, 2.36)	1.48 (1.06, 2.11)	1.48 (0.77, 2.84)	1.66 (1.00, 2.75)	1.85 (1.14, 3.01)
SC IFNB-1a 44 mcg, TIW	0.66 (0.38, 1.15)	0.68 (0.50, 0.93)	0.87 (0.54, 1.36)	0.92 (0.61, 1.38)	0.95 (0.69, 1.32)	0.96 (0.62, 1.49)	1.01 (0.71, 1.42)	**SC IFNB-1a 44 mcg, TIW**	1.01 (0.60, 1.71)	1.02 (0.64, 1.60)	1.09 (0.73, 1.64)	1.28 (0.74, 2.22)	1.49 (0.89, 2.46)	1.49 (0.93, 2.42)	1.49 (0.75, 2.93)	1.67 (1.15, 2.43)	1.86 (1.32, 2.62)

CLAD 5.25mg/kg	0.66 (0.35, 1.22)	0.68 (0.44, 1.03)	0.85 (0.50, 1.47)	0.91 (0.54, 1.54)	0.94 (0.58, 1.54)	0.95 (0.53, 1.71)	0.99 (0.61, 1.62)	0.99 (0.58, 1.67)	**CLAD 5.25mg/kg**	1.01 (0.58, 1.73)	1.08 (0.65, 1.79)	1.27 (0.77, 2.07)	1.47 (0.82, 2.63)	1.47 (0.83, 2.65)	1.47 (0.70, 3.07)	1.65 (0.86, 3.14)	1.83 (0.98, 3.45)
DMF 240 mg, BID	0.65 (0.37, 1.15)	0.67 (0.48, 0.94)	0.85 (0.53, 1.37)	0.90 (0.58, 1.42)	0.93 (0.64, 1.38)	0.95 (0.56, 1.61)	0.99 (0.66, 1.49)	0.98 (0.63, 1.55)	0.99 (0.58, 1.72)	**DMF 240 mg, BID**	1.07 (0.70, 1.66)	1.26 (0.72, 2.21)	1.46 (0.86, 2.47)	1.46 (0.87, 2.50)	1.46 (0.73, 2.93)	1.63 (0.91, 2.97)	1.82 (1.04, 3.24)
FINGO 0.5 mg, QD	0.61 (0.36, 1.03)	0.63 (0.47, 0.82)	0.79 (0.51, 1.22)	0.84 (0.56, 1.27)	0.87 (0.61, 1.24)	0.88 (0.54, 1.44)	0.92 (0.66, 1.28)	0.92 (0.61, 1.38)	0.93 (0.56, 1.54)	0.93 (0.60, 1.44)	**FINGO 0.5 mg, QD**	1.18 (0.69, 1.99)	1.36 (0.83, 2.21)	1.36 (0.87, 2.18)	1.36 (0.70, 2.65)	1.53 (0.88, 2.66)	1.70 (1.00, 2.90)
CLAD 3.5mg/kg	0.52 (0.27, 0.98)	0.53 (0.34, 0.84)	0.67 (0.38, 1.19)	0.72 (0.42, 1.24)	0.74 (0.45, 1.24)	0.75 (0.41, 1.38)	0.78 (0.47, 1.31)	0.78 (0.45, 1.35)	0.79 (0.48, 1.29)	0.79 (0.45, 1.39)	0.85 (0.50, 1.45)	**CLAD 3.5mg/kg**	1.16 (0.63, 2.12)	1.16 (0.64, 2.15)	1.16 (0.55, 2.47)	1.30 (0.67, 2.53)	1.45 (0.77, 2.78)
NAT 300 mg, Q4W	0.45 (0.24, 0.82)	0.46 (0.31, 0.69)	0.58 (0.34, 0.98)	0.62 (0.37, 1.04)	0.64 (0.40, 1.03)	0.65 (0.37, 1.15)	0.68 (0.42, 1.08)	0.67 (0.41, 1.13)	0.68 (0.38, 1.22)	0.69 (0.40, 1.16)	0.73 (0.45, 1.20)	0.86 (0.47, 1.59)	**NAT 300 mg, Q4W**	1.00 (0.57, 1.79)	1.00 (0.48, 2.07)	1.12 (0.60, 2.12)	1.25 (0.68, 2.31)
DAC 150 mg , Q4W	0.45 (0.24, 0.81)	0.46 (0.30, 0.68)	0.58 (0.34, 0.97)	0.62 (0.38, 1.00)	0.64 (0.41, 0.98)	0.65 (0.37, 1.12)	0.68 (0.47, 0.94)	0.67 (0.41, 1.07)	0.68 (0.38, 1.21)	0.69 (0.40, 1.15)	0.73 (0.46, 1.15)	0.86 (0.47, 1.56)	1.00 (0.56, 1.75)	**DAC 150 mg , Q4W**	1.00 (0.48, 2.07)	1.12 (0.61, 2.04)	1.25 (0.69, 2.23)
PEG-INFB-1A 2W 125 mcg, Q2W	0.45 (0.21, 0.95)	0.46 (0.25, 0.84)	0.58 (0.29, 1.16)	0.62 (0.31, 1.22)	0.64 (0.33, 1.23)	0.65 (0.31, 1.35)	0.68 (0.35, 1.30)	0.67 (0.34, 1.33)	0.68 (0.33, 1.42)	0.68 (0.34, 1.37)	0.73 (0.38, 1.43)	0.86 (0.40, 1.83)	1.00 (0.48, 2.07)	1.00 (0.48, 2.08)	**PEG-INFB-1A 2W 125 mcg, Q2W**	1.12 (0.52, 2.45)	1.25 (0.58, 2.70)
OCR 600 mg	0.40 (0.20, 0.78)	0.41 (0.25, 0.67)	0.52 (0.29, 0.93)	0.55 (0.32, 0.96)	0.57 (0.35, 0.94)	0.58 (0.32, 1.03)	0.60 (0.36, 1.00)	0.60 (0.41, 0.87)	0.61 (0.32, 1.16)	0.61 (0.34, 1.10)	0.66 (0.38, 1.14)	0.77 (0.39, 1.49)	0.89 (0.47, 1.67)	0.89 (0.49, 1.65)	0.89 (0.41, 1.94)	**OCR 600 mg**	1.11 (0.67, 1.85)

ALEM 12 mg	0.36 (0.19, 0.68)	0.37 (0.23, 0.58)	0.47 (0.26, 0.82)	0.50 (0.29, 0.84)	0.51 (0.32, 0.82)	0.52 (0.30, 0.90)	0.54 (0.33, 0.87)	0.54 (0.38, 0.75)	0.55 (0.29, 1.02)	0.55 (0.31, 0.96)	0.59 (0.35, 1.00)	0.69 (0.36, 1.31)	0.80 (0.43, 1.46)	0.80 (0.45, 1.45)	0.80 (0.37, 1.71)	0.90 (0.54, 1.49)	**ALEM 12 mg**

Table 16 Input data for MTC Model 2 – ITT analysis

trial_id	base_drug	drug	CDP12_loghr	CDP12_loghrse	CDP24_loghr	CDP24_loghrse
BEYOND	SC IFNB-1b 250 mcg, EOD	GA 20 mg, QD	-0.0548392672444591	0.12911249842632		
Bornstein 1987	Placebo	GA 20 mg, QD	-1.07006061026166	0.543132105986777		
Copolymer 1 MS trial	Placebo	GA 20 mg, QD	-0.148707800188344	0.264002496653078		
HAS Meta Analysis	SC IFNB-1a 44 mcg, TIW	ALEM 12 mg	-0.426305977605486	0.14645097462856		
IFNB MS	Placebo	SC IFNB-1b 250 mcg, EOD	-0.346226952249605	0.205061099518024		
PRISMS	Placebo	SC IFNB-1a 22 mcg, TIW	-0.37708594119886	0.182083282592521		
PRISMS	Placebo	SC IFNB-1a 44 mcg, TIW	-0.469140374882885	0.191239640516145		
TEMSO	Placebo	TERI 7 mg, QD	-0.265514165541755	0.160359351893463		
TRANSFORMS	IM IFNB-1a 30 mcg, QW	FINGO 0.5 mg, QD	-0.3025238717907	0.262412491215324		
CAMMS223	SC IFNB-1a 44 mcg, TIW	ALEM 12 mg			-1.38469691567163	0.419682651794944
CARE-MS I	SC IFNB-1a 44 mcg, TIW	ALEM 12 mg			-0.354638281244914	0.286557372770021
CARE-MS II	SC IFNB-1a 44 mcg, TIW	ALEM 12 mg			-0.553423046797607	0.211306622175561
CombiRx	IM IFNB-1a 30 mcg, QW	GA 20 mg, QD			0.159137103677619	0.189288964606882
MSCRG	Placebo	IM IFNB-1a 30 mcg, QW			-0.551911996333821	0.222248356590701
REGARD	SC IFNB-1a 44 mcg, TIW	GA 20 mg, QD			-0.305221867645457	0.22929195146794

trial_id	base_drug	drug	CDP12_loghr	CDP12_loghrse	CDP24_loghr	CDP24_loghrse
ADVANCE	Placebo	PEG-INFB-1A 2W 125 mcg, Q2W	-0.473374969679432	0.225977429691185	-0.778897339641131	0.289885871594632
AFFIRM	Placebo	NAT 300 mg, Q4W	-0.552667417214468	0.148623802591868	-0.777474863575015	0.168973347421733
BRAVO	Placebo	IM IFNB-1a 30 mcg, QW	-0.293583428511357	0.193755675894086	-0.311997160935814	0.226033379256234
CLARITY	Placebo	CLAD 3.5mg/kg	-0.403269933957518	0.168724102613614	-0.628686790526526	0.200492069900743
CLARITY	Placebo	CLAD 5.25mg/kg	-0.37708594119886	0.171563238101329	-0.392740895881371	0.184837596120746
CONFIRM	Placebo	GA 20 mg, QD	-0.0736123598782625	0.198175050876682	-0.137876750793254	0.234673596919575
CONFIRM	Placebo	DMF 240 mg, BID	-0.239986580141613	0.211193820033189	-0.482346735551161	0.261176294792197
DECIDE	IM IFNB-1a 30 mcg, QW	DAC 150 mg , Q4W	-0.173928397743925	0.123258697049868	-0.30901985403657	0.147355687101556
DEFINE	Placebo	DMF 240 mg, BID	-0.480121309701669	0.17390777671845	-0.26144910250013	0.200243553523742
EVIDENCE	IM IFNB-1a 30 mcg, QW	SC IFNB-1a 44 mcg, TIW	-0.137350019114306	0.207845487922126	-0.359232494272118	0.297130635503228
FREEDOMS	Placebo	FINGO 0.5 mg, QD	-0.34737423096346	0.156404202266941	-0.463170533863828	0.182556131737756
FREEDOMS II	Placebo	FINGO 0.5 mg, QD	-0.190483818253888	0.155006379367802	-0.333155263303193	0.204496893763779
OPERA I	SC IFNB-1a 44 mcg, TIW	OCR 600 mg	-0.549806394500847	0.226758101450521	-0.56505147787974	0.262121522189893
OPERA II	SC IFNB-1a 44 mcg, TIW	OCR 600 mg	-0.475441088321887	0.200030346623896	-0.468246719595837	0.228593883815468
SELECT	Placebo	DAC 150 mg , Q4W	-0.844240559887277	0.365513871621118	-1.43499053412422	0.496405650269213
TEMSO	Placebo	TERI 14 mg, QD	-0.351901880374237	0.164001363719147	-0.284492268969761	0.198394022598982
TOWER	Placebo	TERI 7 mg, QD	-0.0427789441808232	0.174940579913858	0.0525852488027698	0.216147413364083
TOWER	Placebo	TERI 14 mg, QD	-0.377511292139016	0.192607802111743	-0.17052595366143	0.234034643446358

Table 17 Cross tabulation for CDP-12 MTC Model 2 – ITT analysis (hazard ratios and 95% credible intervals)

	Placebo	TERI 7 mg, QD	SC IFNB-1b 250 mcg, EOD	GA 20 mg, QD	FINGO 0.5 mg, QD	IM IFNB-1a 30 mcg, QW	TERI 14 mg, QD	SC IFNB-1a 44 mcg, TIW	DMF 240 mg, BID	CLAD 5.25mg/kg	SC IFNB-1a 22 mcg, TIW	CLAD 3.5mg/kg	PEG-INFB-1A 2W 125 mcg, Q2W	DAC 150 mg , Q4W	NAT 300 mg, Q4W	ALEM 12 mg	OCR 600 mg

Placebo	**Placebo**	1.16 (0.89, 1.49)	1.30 (0.98, 1.73)	1.33 (1.06, 1.67)	1.40 (1.13, 1.74)	1.40 (1.12, 1.74)	1.39 (1.07, 1.80)	1.41 (1.06, 1.87)	1.42 (1.08, 1.88)	1.44 (1.00, 2.05)	1.45 (0.99, 2.14)	1.55 (1.09, 2.20)	1.65 (1.05, 2.61)	1.77 (1.28, 2.44)	1.81 (1.32, 2.49)	2.33 (1.61, 3.38)	2.33 (1.54, 3.54)
TERI 7 mg, QD	0.87 (0.67, 1.12)	**TERI 7 mg, QD**	1.13 (0.77, 1.66)	1.15 (0.82, 1.62)	1.21 (0.87, 1.70)	1.21 (0.86, 1.69)	1.21 (0.84, 1.72)	1.22 (0.84, 1.79)	1.24 (0.85, 1.80)	1.25 (0.81, 1.93)	1.26 (0.79, 1.99)	1.34 (0.87, 2.08)	1.43 (0.86, 2.41)	1.54 (1.02, 2.33)	1.57 (1.04, 2.38)	2.02 (1.30, 3.18)	2.01 (1.26, 3.31)
SC IFNB-1b 250 mcg, EOD	0.77 (0.58, 1.02)	0.89 (0.60, 1.29)	**SC IFNB-1b 250 mcg, EOD**	1.02 (0.79, 1.31)	1.07 (0.75, 1.53)	1.07 (0.76, 1.49)	1.07 (0.72, 1.57)	1.08 (0.74, 1.57)	1.09 (0.73, 1.62)	1.10 (0.69, 1.72)	1.11 (0.69, 1.80)	1.19 (0.75, 1.86)	1.27 (0.74, 2.18)	1.36 (0.90, 2.04)	1.39 (0.90, 2.12)	1.78 (1.16, 2.77)	1.79 (1.10, 2.90)
GA 20 mg, QD	0.75 (0.60, 0.95)	0.87 (0.62, 1.22)	0.98 (0.77, 1.27)	**GA 20 mg, QD**	1.05 (0.78, 1.43)	1.05 (0.80, 1.38)	1.05 (0.74, 1.47)	1.06 (0.78, 1.45)	1.07 (0.75, 1.54)	1.08 (0.71, 1.64)	1.09 (0.70, 1.73)	1.16 (0.77, 1.76)	1.25 (0.74, 2.08)	1.34 (0.93, 1.91)	1.36 (0.93, 2.01)	1.75 (1.20, 2.60)	1.75 (1.13, 2.71)
FINGO 0.5 mg, QD	0.72 (0.58, 0.89)	0.83 (0.59, 1.15)	0.94 (0.66, 1.33)	0.95 (0.70, 1.28)	**FINGO 0.5 mg, QD**	1.00 (0.75, 1.32)	1.00 (0.71, 1.39)	1.01 (0.71, 1.41)	1.02 (0.72, 1.45)	1.03 (0.68, 1.55)	1.04 (0.67, 1.61)	1.10 (0.73, 1.66)	1.18 (0.72, 1.94)	1.27 (0.88, 1.84)	1.29 (0.88, 1.89)	1.67 (1.10, 2.52)	1.67 (1.05, 2.63)
IM IFNB-1a 30 mcg, QW	0.72 (0.57, 0.90)	0.83 (0.59, 1.16)	0.93 (0.67, 1.31)	0.95 (0.72, 1.24)	1.00 (0.76, 1.33)	**IM IFNB-1a 30 mcg, QW**	1.00 (0.71, 1.40)	1.01 (0.76, 1.34)	1.02 (0.72, 1.45)	1.03 (0.67, 1.55)	1.04 (0.66, 1.63)	1.11 (0.73, 1.68)	1.18 (0.71, 1.96)	1.27 (0.98, 1.65)	1.29 (0.89, 1.91)	1.67 (1.16, 2.44)	1.67 (1.10, 2.53)
TERI 14 mg, QD	0.72 (0.56, 0.93)	0.83 (0.58, 1.20)	0.94 (0.64, 1.39)	0.95 (0.68, 1.35)	1.00 (0.72, 1.42)	1.00 (0.72, 1.41)	**TERI 14 mg, QD**	1.01 (0.70, 1.49)	1.02 (0.71, 1.49)	1.03 (0.67, 1.60)	1.04 (0.66, 1.67)	1.11 (0.71, 1.72)	1.19 (0.70, 2.03)	1.28 (0.84, 1.94)	1.30 (0.86, 1.96)	1.67 (1.07, 2.65)	1.67 (1.03, 2.74)
SC IFNB-1a 44 mcg, TIW	0.71 (0.54, 0.94)	0.82 (0.56, 1.19)	0.93 (0.64, 1.35)	0.94 (0.69, 1.28)	0.99 (0.71, 1.40)	0.99 (0.74, 1.31)	0.99 (0.67, 1.44)	**SC IFNB-1a 44**	1.01 (0.69, 1.50)	1.02 (0.65, 1.59)	1.03 (0.63, 1.66)	1.10 (0.70, 1.72)	1.17 (0.68, 1.99)	1.26 (0.86, 1.83)	1.28 (0.85, 1.96)	1.65 (1.29, 2.12)	1.66 (1.21, 2.23)

								mcg, TIW									
DMF 240 mg, BID	0.70 (0.53, 0.93)	0.81 (0.56, 1.18)	0.91 (0.62, 1.37)	0.93 (0.65, 1.34)	0.98 (0.69, 1.40)	0.98 (0.69, 1.39)	0.98 (0.67, 1.42)	0.99 (0.67, 1.46)	**DMF 240 mg, BID**	1.01 (0.64, 1.58)	1.02 (0.64, 1.64)	1.09 (0.69, 1.71)	1.16 (0.68, 1.97)	1.25 (0.81, 1.92)	1.27 (0.83, 1.94)	1.63 (1.03, 2.60)	1.63 (0.99, 2.69)
CLAD 5.25mg/kg	0.69 (0.49, 1.00)	0.80 (0.52, 1.24)	0.91 (0.58, 1.44)	0.92 (0.61, 1.42)	0.97 (0.65, 1.48)	0.97 (0.64, 1.48)	0.97 (0.63, 1.49)	0.98 (0.63, 1.55)	0.99 (0.63, 1.56)	**CLAD 5.25mg/kg**	1.01 (0.60, 1.71)	1.07 (0.65, 1.79)	1.15 (0.65, 2.03)	1.23 (0.77, 2.00)	1.26 (0.79, 2.02)	1.62 (0.98, 2.74)	1.62 (0.95, 2.82)
SC IFNB-1a 22 mcg, TIW	0.69 (0.47, 1.01)	0.80 (0.50, 1.26)	0.90 (0.56, 1.46)	0.92 (0.58, 1.43)	0.96 (0.62, 1.50)	0.96 (0.61, 1.51)	0.96 (0.60, 1.52)	0.97 (0.60, 1.58)	0.98 (0.61, 1.57)	0.99 (0.59, 1.67)	**SC IFNB-1a 22 mcg, TIW**	1.07 (0.63, 1.81)	1.13 (0.63, 2.05)	1.22 (0.74, 2.02)	1.25 (0.76, 2.05)	1.59 (0.94, 2.76)	1.60 (0.91, 2.85)
CLAD 3.5mg/kg	0.65 (0.45, 0.92)	0.75 (0.48, 1.15)	0.84 (0.54, 1.33)	0.86 (0.57, 1.31)	0.91 (0.60, 1.37)	0.90 (0.59, 1.36)	0.90 (0.58, 1.40)	0.91 (0.58, 1.42)	0.92 (0.59, 1.45)	0.93 (0.56, 1.53)	0.94 (0.55, 1.59)	**CLAD 3.5mg/kg**	1.07 (0.60, 1.89)	1.15 (0.72, 1.84)	1.17 (0.73, 1.88)	1.51 (0.91, 2.51)	1.51 (0.88, 2.58)
PEG-INFB-1A 2W 125 mcg, Q2W	0.61 (0.38, 0.95)	0.70 (0.42, 1.16)	0.79 (0.46, 1.35)	0.80 (0.48, 1.35)	0.85 (0.51, 1.39)	0.84 (0.51, 1.40)	0.84 (0.49, 1.42)	0.85 (0.50, 1.47)	0.86 (0.51, 1.47)	0.87 (0.49, 1.55)	0.88 (0.49, 1.59)	0.94 (0.53, 1.66)	**PEG-INFB-1A 2W 125 mcg, Q2W**	1.08 (0.61, 1.86)	1.09 (0.63, 1.90)	1.41 (0.79, 2.53)	1.41 (0.76, 2.63)
DAC 150 mg , Q4W	0.56 (0.41, 0.78)	0.65 (0.43, 0.98)	0.74 (0.49, 1.11)	0.75 (0.52, 1.07)	0.79 (0.54, 1.14)	0.79 (0.61, 1.02)	0.78 (0.52, 1.19)	0.80 (0.55, 1.16)	0.80 (0.52, 1.23)	0.81 (0.50, 1.29)	0.82 (0.49, 1.36)	0.87 (0.54, 1.40)	0.93 (0.54, 1.63)	**DAC 150 mg , Q4W**	1.02 (0.66, 1.60)	1.31 (0.85, 2.05)	1.32 (0.81, 2.14)
NAT 300 mg, Q4W	0.55 (0.40, 0.76)	0.64 (0.42, 0.96)	0.72 (0.47, 1.11)	0.73 (0.50, 1.08)	0.77 (0.53, 1.13)	0.77 (0.52, 1.13)	0.77 (0.51, 1.16)	0.78 (0.51, 1.17)	0.79 (0.52, 1.20)	0.80 (0.50, 1.27)	0.80 (0.49, 1.32)	0.86 (0.53, 1.36)	0.91 (0.53, 1.58)	0.98 (0.63, 1.51)	**NAT 300 mg, Q4W**	1.29 (0.80, 2.06)	1.29 (0.76, 2.15)

ALEM 12 mg	0.43 (0.30, 0.62)	0.49 (0.31, 0.77)	0.56 (0.36, 0.87)	0.57 (0.39, 0.83)	0.60 (0.40, 0.91)	0.60 (0.41, 0.86)	0.60 (0.38, 0.93)	0.61 (0.47, 0.78)	0.61 (0.38, 0.97)	0.62 (0.36, 1.02)	0.63 (0.36, 1.06)	0.66 (0.40, 1.10)	0.71 (0.39, 1.26)	0.76 (0.49, 1.18)	0.78 (0.48, 1.25)	**ALEM 12 mg**	1.00 (0.68, 1.48)
OCR 600 mg	0.43 (0.28, 0.65)	0.50 (0.30, 0.79)	0.56 (0.35, 0.91)	0.57 (0.37, 0.89)	0.60 (0.38, 0.95)	0.60 (0.39, 0.91)	0.60 (0.36, 0.97)	0.60 (0.45, 0.82)	0.61 (0.37, 1.01)	0.62 (0.36, 1.05)	0.62 (0.35, 1.10)	0.66 (0.39, 1.14)	0.71 (0.38, 1.31)	0.76 (0.47, 1.24)	0.78 (0.47, 1.31)	1.00 (0.68, 1.47)	**OCR 600 mg**

Table 18 Cross tabulation for CDP-24 MTC Model 2 – ITT analysis (hazard ratios and 95% credible intervals)

	Placebo	**TERI 7 mg, QD**	**TERI 14 mg, QD**	**SC IFNB-1b 250 mcg, EOD**	**GA 20 mg, QD**	**IM IFNB-1a 30 mcg, QW**	**SC IFNB-1a 44 mcg, TIW**	**DMF 240 mg, BID**	**FINGO 0.5 mg, QD**	**CLAD 5.25mg/kg**	**SC IFNB-1a 22 mcg, TIW**	**CLAD 3.5mg/kg**	**PEG-INFB-1A 2W 125 mcg, Q2W**	**DAC 150 mg , Q4W**	**NAT 300 mg, Q4W**	**OCR 600 mg**	**ALEM 12 mg**
Placebo	**Placebo**	1.20 (0.88, 1.61)	1.41 (1.06, 1.88)	1.40 (0.99, 1.99)	1.43 (1.12, 1.84)	1.47 (1.16, 1.86)	1.48 (1.08, 2.01)	1.49 (1.10, 2.01)	1.52 (1.19, 1.95)	1.53 (1.06, 2.19)	1.56 (1.01, 2.41)	1.71 (1.18, 2.47)	1.82 (1.13, 2.95)	1.99 (1.41, 2.80)	2.01 (1.43, 2.80)	2.49 (1.62, 3.85)	2.55 (1.73, 3.75)
TERI 7 mg, QD	0.83 (0.62, 1.14)	**TERI 7 mg, QD**	1.18 (0.79, 1.75)	1.16 (0.76, 1.86)	1.20 (0.83, 1.75)	1.23 (0.85, 1.78)	1.24 (0.82, 1.89)	1.24 (0.82, 1.87)	1.27 (0.87, 1.86)	1.27 (0.80, 2.02)	1.30 (0.78, 2.19)	1.42 (0.89, 2.30)	1.52 (0.88, 2.67)	1.65 (1.06, 2.60)	1.67 (1.07, 2.65)	2.07 (1.26, 3.52)	2.13 (1.34, 3.46)
TERI 14 mg, QD	0.71 (0.53, 0.95)	0.85 (0.57, 1.27)	**TERI 14 mg, QD**	0.99 (0.64, 1.56)	1.01 (0.71, 1.47)	1.04 (0.73, 1.49)	1.05 (0.70, 1.58)	1.05 (0.71, 1.58)	1.08 (0.75, 1.57)	1.08 (0.69, 1.70)	1.10 (0.67, 1.85)	1.21 (0.75, 1.93)	1.29 (0.74, 2.27)	1.40 (0.90, 2.20)	1.42 (0.92, 2.20)	1.75 (1.07, 2.95)	1.80 (1.13, 2.89)
SC IFNB-1b 250 mcg, EOD	0.71 (0.50, 1.01)	0.86 (0.54, 1.32)	1.01 (0.64, 1.56)	**SC IFNB-1b 250 mcg, EOD**	1.02 (0.73, 1.41)	1.05 (0.72, 1.53)	1.06 (0.69, 1.61)	1.06 (0.67, 1.65)	1.08 (0.72, 1.64)	1.09 (0.67, 1.77)	1.11 (0.65, 1.90)	1.22 (0.74, 2.00)	1.30 (0.73, 2.34)	1.41 (0.90, 2.24)	1.43 (0.89, 2.31)	1.78 (1.05, 2.99)	1.82 (1.13, 2.93)

GA 20 mg, QD	0.70 (0.54, 0.90)	0.84 (0.57, 1.21)	0.99 (0.68, 1.41)	0.98 (0.71, 1.37)	**GA 20 mg, QD**	1.03 (0.79, 1.34)	1.04 (0.76, 1.42)	1.04 (0.71, 1.51)	1.06 (0.77, 1.48)	1.06 (0.69, 1.64)	1.09 (0.67, 1.77)	1.19 (0.77, 1.84)	1.27 (0.74, 2.17)	1.38 (0.96, 2.00)	1.40 (0.94, 2.11)	1.73 (1.11, 2.71)	1.78 (1.21, 2.62)
IM IFNB-1a 30 mcg, QW	0.68 (0.54, 0.86)	0.81 (0.56, 1.17)	0.96 (0.67, 1.37)	0.95 (0.66, 1.39)	0.97 (0.75, 1.26)	**IM IFNB-1a 30 mcg, QW**	1.01 (0.74, 1.37)	1.01 (0.70, 1.46)	1.03 (0.76, 1.41)	1.04 (0.67, 1.58)	1.06 (0.65, 1.72)	1.16 (0.75, 1.78)	1.24 (0.74, 2.09)	1.34 (1.02, 1.79)	1.36 (0.92, 2.03)	1.69 (1.09, 2.61)	1.73 (1.18, 2.54)
SC IFNB-1a 44 mcg, TIW	0.67 (0.50, 0.93)	0.81 (0.53, 1.21)	0.96 (0.63, 1.42)	0.94 (0.62, 1.45)	0.97 (0.71, 1.32)	0.99 (0.73, 1.35)	**SC IFNB-1a 44 mcg, TIW**	1.00 (0.67, 1.52)	1.02 (0.71, 1.50)	1.03 (0.64, 1.63)	1.05 (0.62, 1.76)	1.15 (0.72, 1.84)	1.23 (0.70, 2.13)	1.34 (0.89, 2.00)	1.35 (0.88, 2.11)	1.68 (1.21, 2.30)	1.72 (1.34, 2.21)
DMF 240 mg, BID	0.67 (0.50, 0.91)	0.80 (0.53, 1.21)	0.95 (0.63, 1.41)	0.94 (0.61, 1.49)	0.96 (0.66, 1.40)	0.99 (0.68, 1.43)	1.00 (0.66, 1.50)	**DMF 240 mg, BID**	1.02 (0.70, 1.49)	1.03 (0.64, 1.63)	1.05 (0.63, 1.76)	1.15 (0.71, 1.84)	1.23 (0.70, 2.14)	1.33 (0.85, 2.10)	1.35 (0.87, 2.10)	1.67 (0.99, 2.80)	1.71 (1.07, 2.75)
FINGO 0.5 mg, QD	0.66 (0.51, 0.84)	0.79 (0.54, 1.15)	0.93 (0.64, 1.34)	0.92 (0.61, 1.38)	0.94 (0.68, 1.30)	0.97 (0.71, 1.31)	0.98 (0.67, 1.40)	0.98 (0.67, 1.43)	**FINGO 0.5 mg, QD**	1.00 (0.65, 1.54)	1.02 (0.63, 1.66)	1.12 (0.72, 1.72)	1.20 (0.71, 2.02)	1.30 (0.88, 1.93)	1.32 (0.88, 1.97)	1.63 (1.01, 2.65)	1.67 (1.08, 2.57)
CLAD 5.25mg/kg	0.65 (0.46, 0.95)	0.79 (0.49, 1.25)	0.93 (0.59, 1.46)	0.92 (0.57, 1.50)	0.94 (0.61, 1.45)	0.96 (0.63, 1.49)	0.97 (0.61, 1.57)	0.97 (0.61, 1.56)	1.00 (0.65, 1.54)	**CLAD 5.25mg/kg**	1.02 (0.58, 1.80)	1.12 (0.67, 1.88)	1.20 (0.66, 2.15)	1.30 (0.80, 2.13)	1.31 (0.81, 2.13)	1.62 (0.94, 2.89)	1.67 (1.00, 2.83)
SC IFNB-1a 22 mcg, TIW	0.64 (0.42, 0.99)	0.77 (0.46, 1.29)	0.91 (0.54, 1.50)	0.90 (0.53, 1.54)	0.92 (0.56, 1.50)	0.95 (0.58, 1.54)	0.95 (0.57, 1.61)	0.96 (0.57, 1.59)	0.98 (0.60, 1.60)	0.98 (0.56, 1.71)	**SC IFNB-1a 22 mcg, TIW**	1.10 (0.62, 1.93)	1.17 (0.62, 2.20)	1.28 (0.74, 2.21)	1.29 (0.75, 2.20)	1.60 (0.88, 2.93)	1.63 (0.94, 2.90)

CLAD 3.5mg/kg	0.59 (0.40, 0.85)	0.70 (0.43, 1.12)	0.83 (0.52, 1.33)	0.82 (0.50, 1.35)	0.84 (0.54, 1.30)	0.86 (0.56, 1.33)	0.87 (0.54, 1.39)	0.87 (0.54, 1.41)	0.89 (0.58, 1.38)	0.89 (0.53, 1.50)	0.91 (0.52, 1.60)	**CLAD 3.5mg/kg**	1.07 (0.59, 1.93)	1.16 (0.71, 1.90)	1.17 (0.72, 1.91)	1.46 (0.83, 2.55)	1.50 (0.89, 2.52)
PEG-INFB-1A 2W 125 mcg, Q2W	0.55 (0.34, 0.89)	0.66 (0.38, 1.13)	0.78 (0.44, 1.35)	0.77 (0.43, 1.36)	0.78 (0.46, 1.34)	0.81 (0.48, 1.36)	0.81 (0.47, 1.44)	0.82 (0.47, 1.43)	0.84 (0.50, 1.41)	0.84 (0.47, 1.52)	0.86 (0.45, 1.62)	0.94 (0.52, 1.69)	**PEG-INFB-1A 2W 125 mcg, Q2W**	1.09 (0.61, 1.92)	1.10 (0.62, 1.95)	1.36 (0.72, 2.59)	1.39 (0.77, 2.56)
DAC 150 mg , Q4W	0.50 (0.36, 0.71)	0.60 (0.38, 0.94)	0.71 (0.45, 1.11)	0.71 (0.45, 1.11)	0.72 (0.50, 1.05)	0.74 (0.56, 0.98)	0.75 (0.50, 1.12)	0.75 (0.48, 1.18)	0.77 (0.52, 1.14)	0.77 (0.47, 1.25)	0.78 (0.45, 1.35)	0.86 (0.53, 1.40)	0.92 (0.52, 1.65)	**DAC 150 mg , Q4W**	1.01 (0.64, 1.61)	1.25 (0.75, 2.09)	1.29 (0.81, 2.03)
NAT 300 mg, Q4W	0.50 (0.36, 0.70)	0.60 (0.38, 0.93)	0.71 (0.45, 1.09)	0.70 (0.43, 1.12)	0.71 (0.47, 1.07)	0.74 (0.49, 1.09)	0.74 (0.47, 1.14)	0.74 (0.48, 1.16)	0.76 (0.51, 1.14)	0.76 (0.47, 1.24)	0.78 (0.45, 1.33)	0.85 (0.52, 1.38)	0.91 (0.51, 1.61)	0.99 (0.62, 1.57)	**NAT 300 mg, Q4W**	1.24 (0.72, 2.11)	1.27 (0.78, 2.06)
OCR 600 mg	0.40 (0.26, 0.62)	0.48 (0.28, 0.80)	0.57 (0.34, 0.94)	0.56 (0.33, 0.95)	0.58 (0.37, 0.90)	0.59 (0.38, 0.92)	0.60 (0.43, 0.83)	0.60 (0.36, 1.01)	0.61 (0.38, 0.99)	0.62 (0.35, 1.06)	0.63 (0.34, 1.14)	0.69 (0.39, 1.20)	0.73 (0.39, 1.38)	0.80 (0.48, 1.33)	0.81 (0.47, 1.39)	**OCR 600 mg**	1.03 (0.69, 1.53)
ALEM 12 mg	0.39 (0.27, 0.58)	0.47 (0.29, 0.75)	0.56 (0.35, 0.88)	0.55 (0.34, 0.88)	0.56 (0.38, 0.82)	0.58 (0.39, 0.85)	0.58 (0.45, 0.75)	0.59 (0.36, 0.94)	0.60 (0.39, 0.92)	0.60 (0.35, 1.00)	0.61 (0.34, 1.07)	0.67 (0.40, 1.13)	0.72 (0.39, 1.29)	0.78 (0.49, 1.23)	0.79 (0.49, 1.29)	0.97 (0.65, 1.45)	**ALEM 12 mg**

Table 19 Cross tabulation for MTC Model 1 – HA subgroup (hazard ratios and 95% credible intervals)

	Placebo	**SC IFNB-1b 250 mcg, EOD**	**SC IFNB-1a 22 mcg, TIW**	**GA 20 mg, QD**	**IM IFNB-1a 30 mcg, QW**	**SC IFNB-1a 44 mcg, TIW**	**FINGO 0.5 mg, QD**	**DAC 150 mg , Q4W**	**ALEM 12 mg**	**OCR 600 mg**

Placebo	**Placebo**	1.37 (0.98, 1.92)	1.41 (0.92, 2.19)	1.42 (1.10, 1.85)	1.47 (1.12, 1.92)	1.47 (1.06, 2.05)	1.95 (1.22, 3.15)	2.66 (1.54, 4.62)	2.69 (1.41, 5.20)	2.95 (1.20, 7.12)
SC IFNB-1b 250 mcg, EOD	0.73 (0.52, 1.02)	**SC IFNB-1b 250 mcg, EOD**	1.03 (0.61, 1.77)	1.04 (0.76, 1.41)	1.07 (0.72, 1.59)	1.08 (0.70, 1.65)	1.43 (0.81, 2.55)	1.94 (1.04, 3.63)	1.97 (0.97, 4.00)	2.15 (0.85, 5.44)
SC IFNB-1a 22 mcg, TIW	0.71 (0.46, 1.08)	0.97 (0.56, 1.65)	**SC IFNB-1a 22 mcg, TIW**	1.00 (0.62, 1.63)	1.04 (0.63, 1.68)	1.04 (0.65, 1.67)	1.38 (0.73, 2.61)	1.88 (0.93, 3.74)	1.90 (0.91, 3.94)	2.08 (0.80, 5.34)
GA 20 mg, QD	0.70 (0.54, 0.91)	0.96 (0.71, 1.31)	1.00 (0.62, 1.62)	**GA 20 mg, QD**	1.03 (0.76, 1.39)	1.04 (0.73, 1.46)	1.38 (0.81, 2.34)	1.87 (1.05, 3.31)	1.89 (0.98, 3.68)	2.07 (0.84, 5.06)
IM IFNB-1a 30 mcg, QW	0.68 (0.52, 0.90)	0.93 (0.63, 1.40)	0.96 (0.59, 1.59)	0.97 (0.72, 1.32)	**IM IFNB-1a 30 mcg, QW**	1.00 (0.70, 1.45)	1.33 (0.81, 2.22)	1.81 (1.11, 2.95)	1.83 (0.94, 3.62)	2.00 (0.81, 4.96)
SC IFNB-1a 44 mcg, TIW	0.68 (0.49, 0.94)	0.93 (0.61, 1.43)	0.96 (0.60, 1.55)	0.96 (0.68, 1.36)	1.00 (0.69, 1.43)	**SC IFNB-1a 44 mcg, TIW**	1.33 (0.75, 2.33)	1.81 (0.98, 3.29)	1.83 (1.04, 3.23)	2.00 (0.87, 4.53)
FINGO 0.5 mg, QD	0.51 (0.32, 0.82)	0.70 (0.39, 1.24)	0.72 (0.38, 1.37)	0.73 (0.43, 1.23)	0.75 (0.45, 1.24)	0.75 (0.43, 1.33)	**FINGO 0.5 mg, QD**	1.36 (0.67, 2.74)	1.37 (0.62, 3.08)	1.51 (0.55, 4.06)
DAC 150 mg , Q4W	0.38 (0.22, 0.65)	0.52 (0.28, 0.96)	0.53 (0.27, 1.07)	0.53 (0.30, 0.95)	0.55 (0.34, 0.90)	0.55 (0.30, 1.02)	0.74 (0.37, 1.50)	**DAC 150 mg , Q4W**	1.01 (0.44, 2.33)	1.11 (0.40, 3.09)
ALEM 12 mg	0.37 (0.19, 0.71)	0.51 (0.25, 1.04)	0.53 (0.25, 1.10)	0.53 (0.27, 1.02)	0.55 (0.28, 1.06)	0.55 (0.31, 0.96)	0.73 (0.32, 1.61)	0.99 (0.43, 2.25)	**ALEM 12 mg**	1.09 (0.40, 2.96)
OCR 600 mg	0.34 (0.14, 0.83)	0.47 (0.18, 1.18)	0.48 (0.19, 1.25)	0.48 (0.20, 1.19)	0.50 (0.20, 1.23)	0.50 (0.22, 1.15)	0.66 (0.25, 1.82)	0.90 (0.32, 2.51)	0.91 (0.34, 2.50)	**OCR 600 mg**

Table 20 Cross tabulation for MTC Model 1 – RES subgroup (hazard ratios and 95% credible intervals)

	Placebo	SC IFNB-1b 250 mcg, EOD	SC IFNB-1a 22 mcg, TIW	GA 20 mg, QD	SC IFNB-1a 44 mcg, TIW	IM IFNB-1a 30 mcg, QW	OCR 600 mg	ALEM 12 mg	NAT 300 mg, Q4W	DAC 150 mg , Q4W
Placebo	**Placebo**	1.37 (0.98, 1.93)	1.42 (0.92, 2.21)	1.43 (1.11, 1.86)	1.48 (1.06, 2.07)	1.49 (1.11, 1.98)	2.41 (1.06, 5.45)	2.56 (0.99, 6.61)	2.79 (1.25, 6.13)	8.30 (0.91, 73.51)
SC IFNB-1b 250 mcg, EOD	0.73 (0.52, 1.02)	**SC IFNB-1b 250 mcg, EOD**	1.03 (0.60, 1.78)	1.04 (0.76, 1.42)	1.08 (0.70, 1.66)	1.09 (0.72, 1.61)	1.75 (0.74, 4.14)	1.87 (0.70, 4.98)	2.03 (0.85, 4.77)	6.06 (0.66, 55.30)
SC IFNB-1a 22 mcg, TIW	0.71 (0.45, 1.09)	0.97 (0.56, 1.66)	**SC IFNB-1a 22 mcg, TIW**	1.01 (0.61, 1.64)	1.04 (0.64, 1.70)	1.05 (0.63, 1.73)	1.70 (0.70, 4.14)	1.80 (0.66, 4.93)	1.96 (0.78, 4.83)	5.87 (0.61, 54.21)
GA 20 mg, QD	0.70 (0.54, 0.90)	0.96 (0.70, 1.31)	0.99 (0.61, 1.63)	**GA 20 mg, QD**	1.04 (0.73, 1.47)	1.04 (0.76, 1.41)	1.69 (0.74, 3.83)	1.79 (0.69, 4.64)	1.95 (0.84, 4.49)	5.83 (0.63, 52.14)
SC IFNB-1a 44 mcg, TIW	0.68 (0.48, 0.94)	0.93 (0.60, 1.43)	0.96 (0.59, 1.56)	0.97 (0.68, 1.37)	**SC IFNB-1a 44 mcg, TIW**	1.01 (0.69, 1.45)	1.63 (0.78, 3.42)	1.73 (0.72, 4.15)	1.89 (0.79, 4.42)	5.64 (0.61, 50.49)
IM IFNB-1a 30 mcg, QW	0.67 (0.51, 0.90)	0.92 (0.62, 1.39)	0.95 (0.58, 1.60)	0.96 (0.71, 1.32)	0.99 (0.69, 1.45)	**IM IFNB-1a 30 mcg, QW**	1.62 (0.71, 3.75)	1.72 (0.66, 4.49)	1.87 (0.80, 4.34)	5.60 (0.61, 50.22)
OCR 600 mg	0.42 (0.18, 0.94)	0.57 (0.24, 1.35)	0.59 (0.24, 1.43)	0.59 (0.26, 1.34)	0.61 (0.29, 1.29)	0.62 (0.27, 1.41)	**OCR 600 mg**	1.06 (0.34, 3.37)	1.16 (0.37, 3.59)	3.46 (0.33, 35.20)
ALEM 12 mg	0.39 (0.15, 1.01)	0.54 (0.20, 1.44)	0.55 (0.20, 1.52)	0.56 (0.22, 1.44)	0.58 (0.24, 1.39)	0.58 (0.22, 1.52)	0.94 (0.30, 2.98)	**ALEM 12 mg**	1.09 (0.32, 3.75)	3.26 (0.29, 35.28)
NAT 300 mg, Q4W	0.36 (0.16, 0.80)	0.49 (0.21, 1.18)	0.51 (0.21, 1.28)	0.51 (0.22, 1.20)	0.53 (0.23, 1.27)	0.53 (0.23, 1.25)	0.86 (0.28, 2.71)	0.92 (0.27, 3.16)	**NAT 300 mg, Q4W**	2.99 (0.29, 30.05)

DAC 150 mg , Q4W	0.12 (0.01, 1.10)	0.17 (0.02, 1.52)	0.17 (0.02, 1.63)	0.17 (0.02, 1.58)	0.18 (0.02, 1.64)	0.18 (0.02, 1.65)	0.29 (0.03, 3.01)	0.31 (0.03, 3.43)	0.33 (0.03, 3.50)	**DAC 150 mg , Q4W**

JAGS Code for MTC Model 2

```
##############################################
# TREATMENT DECODE                           #
##############################################
# t = 1 : Placebo
# t = 2 : ALEM 12 mg
# t = 3 : CLAD 3.5mg/kg
# t = 4 : CLAD 5.25mg/kg
# t = 5 : DAC 150 mg , Q4W
# t = 6 : DMF 240 mg, BID
# t = 7 : FINGO 0.5 mg, QD
# t = 8 : GA 20 mg, QD
# t = 9 : IM IFNB-1a 30 mcg, QW
# t = 10 : NAT 300 mg, Q4W
# t = 11 : OCR 600 mg
# t = 12 : PEG-INFB-1A 2W 125 mcg, Q2W
# t = 13 : SC IFNB-1a 22 mcg, TIW
# t = 14 : SC IFNB-1a 44 mcg, TIW
# t = 15 : SC IFNB-1b 250 mcg, EOD
# t = 16 : TERI 14 mg, QD
# t = 17 : TERI 7 mg, QD
##############################################
# DATA                                       #
##############################################
list(
ns1  =  9 ,
ns2  =  6 ,
ns3  =  18 ,
nt  =  17 ,
pw  =  0.72 ,
se  = structure(.Data =  c(0.1291, NA, 0.5431, NA, 0.264, NA, 0.1465, NA,
0.2051, NA, 0.1821, NA, 0.1912, NA, 0.1604, NA, 0.2624, NA, NA, 0.4197, NA,
0.2866, NA, 0.2113, NA, 0.1893, NA, 0.2222, NA, 0.2293, 0.226, 0.2899,
0.1486, 0.169, 0.1938, 0.226, 0.1687, 0.2005, 0.1716, 0.1848, 0.1982,
0.2347, 0.2112, 0.2612, 0.1233, 0.1474, 0.1739, 0.2002, 0.2078, 0.2971,
0.1564, 0.1826, 0.155, 0.2045, 0.2268, 0.2621, 0.2, 0.2286, 0.3655, 0.4964,
0.164, 0.1984, 0.1749, 0.2161, 0.1926, 0.234) ,.Dim =  c(33, 2) ) ,
t  = structure(.Data =  c(15, 8, 1, 8, 1, 8, 14, 2, 1, 15, 1, 13, 1, 14, 1,
17, 9, 7, 14, 2, 14, 2, 14, 2, 9, 8, 1, 9, 14, 8, 1, 12, 1, 10, 1, 9, 1, 3,
1, 4, 1, 8, 1, 6, 9, 5, 1, 6, 9, 14, 1, 7, 1, 7, 14, 11, 14, 11, 1, 5, 1,
16, 1, 17, 1, 16) ,.Dim =  c(33, 2) ) ,
taulmn  =  -3.95 ,
taulprec  =  0.3121 ,
tauuup  =  5 ,
usevag  =  0 ,
y  = structure(.Data =  c(-0.05484, NA, -1.07, NA, -0.1487, NA, -0.4263,
NA, -0.3462, NA, -0.3771, NA, -0.4691, NA, -0.2655, NA, -0.3025, NA, NA, -
1.385, NA, -0.3546, NA, -0.5534, NA, 0.1591, NA, -0.5519, NA, -0.3052, -
0.4734, -0.7789, -0.5527, -0.7775, -0.2936, -0.312, -0.4033, -0.6287, -
0.3771, -0.3927, -0.07361, -0.1379, -0.24, -0.4823, -0.1739, -0.309, -
0.4801, -0.2614, -0.1374, -0.3592, -0.3474, -0.4632, -0.1905, -0.3332, -
0.5498, -0.5651, -0.4754, -0.4682, -0.8442, -1.435, -0.3519, -0.2845, -
0.04278, 0.05259, -0.3775,
-0.1705) ,.Dim =  c(33, 2) )
)

##############################################
# MODEL                                      #
##############################################
```

```
model
{
for(i in 1:ns1){
vr[i,1] <- pow(se[i,1],2)
prec[i,1] <- 1/vr[i,1]
y[i,1] ~ dnorm(delta[i,1], prec[i,1])
}


for(i in (ns1+1):(ns1 + ns2)) {
vr[i,2] <- pow(se[i,2], 2)
prec[i,2] <- 1/vr[i,2]
y[i,2] ~ dnorm(delta[i,2], prec[i,2])
}

for(i in (ns1 + ns2 + 1):(ns1 + ns2  + ns3)){
for (k in 1:2){
for (j in 1:2){
Sigma[i,j,k] <- se[i,k]*se[i,j]*pw*(1-equals(j,k)) +
pow(se[i,k],2)*equals(j,k)
}
}
PREC[i,1:2,1:2] <- inverse(Sigma[i,1:2,1:2])
y[i,1:2] ~ dmnorm(delta[i,1:2], PREC[i,1:2,1:2])
}



for(i in 1:(ns1 + ns2  + ns3)) {
delta[i,1:2] ~ dmnorm(mu[i,1:2], tau[i,1:2,1:2])
mu[i,1] <- beta[t[i,2], 1] - beta[t[i,1], 1]
mu[i,2] <- beta[t[i,2], 2] - beta[t[i,1], 2]
sig[i,1,1] <-  pow(sd[1], 2)
sig[i,2,2] <- pow(sd[2], 2)
sig[i,1,2] <- sd[1]*sd[2]*pb
sig[i,2,1] <- sd[1]*sd[2]*pb
tau[i,1:2,1:2] <- inverse(sig[i,1:2,1:2])
}


beta[1,1]<-0
beta[1,2]<-0

for (k in 2:nt){
tmp[k,1] <- alpha[k] + gamma[1]
tmp[k,2] <- alpha[k] + gamma[2]

beta[k,1] ~ dnorm(tmp[k,1], T)
beta[k,2] ~ dnorm(tmp[k,2], T)

alpha[k] ~ dnorm(0, 0.0001)
}


gamma[1] ~ dnorm(0,0.0001)
gamma[2] ~ dnorm(0,0.0001)
```

```
sdvag  ~ dunif(0,tauuup)
sdinf2 ~ dlnorm(taulmn,taulprec)
T <-  usevag*pow(sdvag,-2) + (1-usevag)*pow(sdinf2,-1)

for (k in 1:2){
sd[k] ~ dunif(0,2)
}
pb ~ dunif(-1,1)

}
##############################################
```

Table 21: Incremental analysis, new base case ITT (based on ocrelizumab new PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
PegIFNB-1a	[redacted]	[redacted]						
Glatiramer acetate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
IFNB-1a (Avonex)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
IFNB-1b	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
Alemtuzumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	11,148	11,148
IFNB-1a (Rebif)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	51,668	Dominated
Teriflunomide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
Dimethyl fumarate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
Fingolimod*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
Natalizumab*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	124,261	Dominated

* Outside of NICE scope for this population. ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Figure 14 Cost-effectiveness acceptability curve, ITT including alemtuzumab (based on new ocrelizumab PAS)

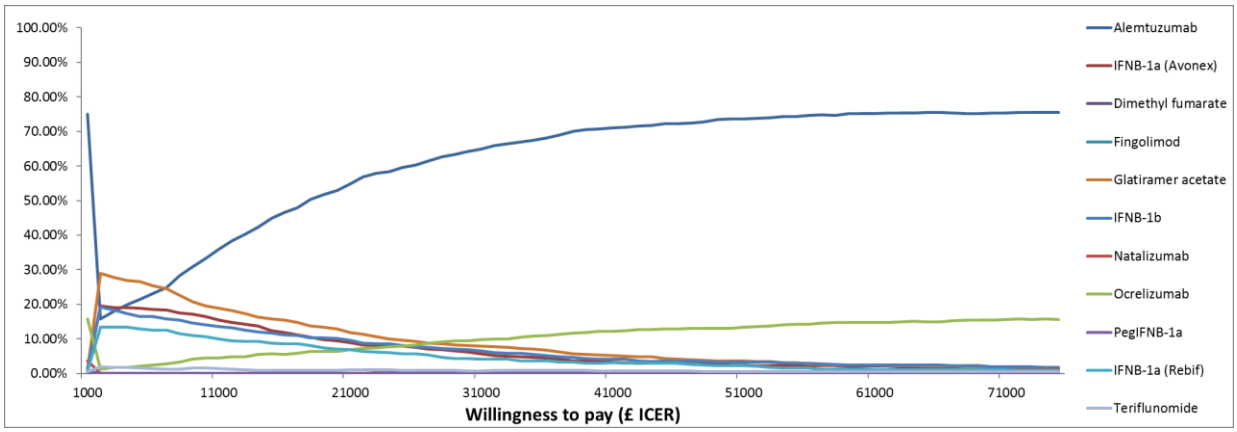
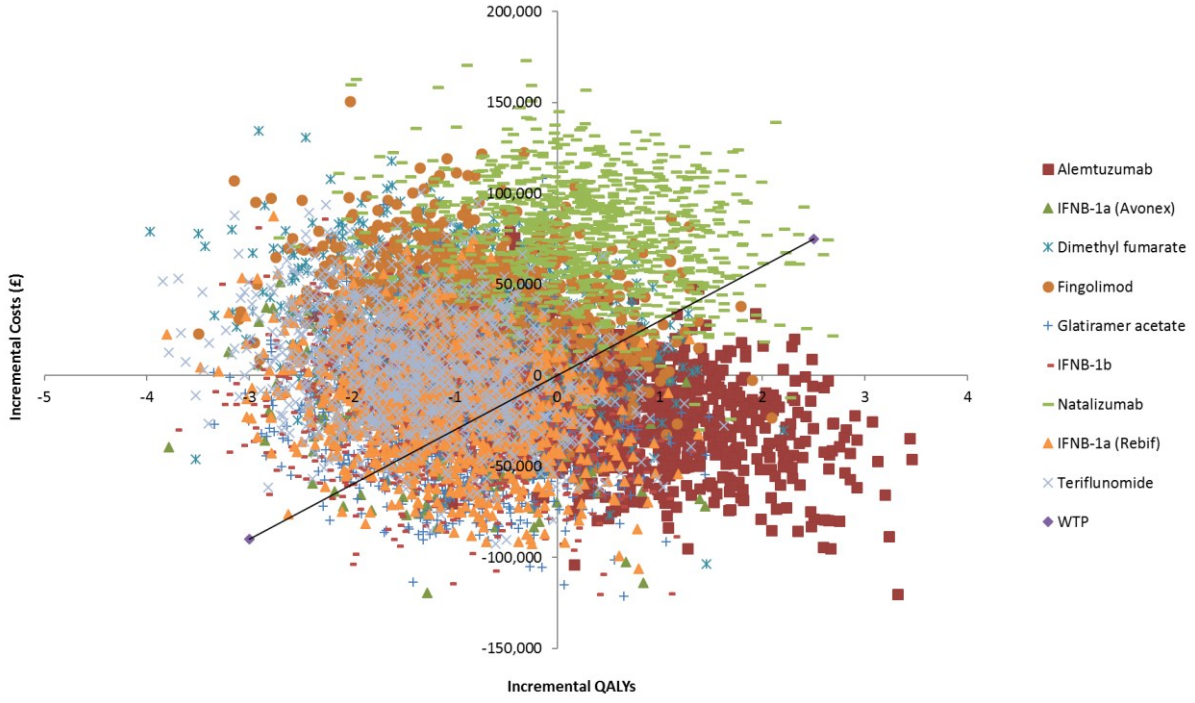


Figure 15 Cost-effectiveness plane for DMTs compared to ocrelizumab, ITT including alemtuzumab (based on new ocrelizumab PAS)



CONFIDENTIAL UNTIL PUBLISHED

Single technology appraisal

Ocrelizumab for treating relapsing multiple sclerosis

Addendum 3 to the ERG report: Critique of the company's updated submission after the first ACD

Confidential: Ocrelizumab PAS analyses (comparator list prices)

Produced by Southampton Health Technology Assessments Centre (SHTAC)

Addendum date 8th May 2018

Commercial in confidence information relating to the ocrelizumab Patient Access Scheme is underlined and highlighted in blue for ocrelizumab.

1 Introduction

The company provided additional evidence to NICE in response to the first Appraisal Consultation Document (ACD). The company's additional evidence (received by the ERG on 26th April 2018) differs from that included in their original submission in the following respects:

- The company has provided additional post-hoc supporting data from the OPERA pivotal trials, for disability progression confirmed after 36 weeks (CDP36) and for disability progression confirmed after 48 weeks (CDP48).
- The company has used two alternative approaches to handle missing data for disability progression confirmed after 24 weeks (CDP24) in their mixed treatment comparison (MTC):
    - Model 1: The missing data for CDP24 were imputed using corresponding data for disability progression confirmed after 12 weeks (CDP12);
    - Model 2: The CDP24 and CDP12 outcomes were jointly modelled using an extension of the Bayesian MTC analysis based on an assumption of exchangeability of treatment effects on the outcomes.
- The company has updated their base case cost-effectiveness analysis, to:
    - include an updated patient access scheme (PAS);
    - include CDP24 estimates from the MTC analysis based on imputation of missing data (Model 1, with model 2 explored in a scenario analysis);
    - include a risk of progressive multifocal leukoencephalopathy (PML) with ocrelizumab (OCR);
    - use the UK MS Survey as a source of Expanded Disability Status Scale (EDSS)-based costs;

The NICE committee also expressed a preference for the inclusion of treatment stopping rates for OCR and comparators in the absence of evidence of waning of treatment effect. However, this was already included in the company's previous base case analysis.

This addendum presents a brief critique of the company's additional evidence, and includes additional analyses conducted by the ERG as requested by NICE to address concerns and uncertainties raised in the ACD.

2 Analyses of disability progression

In their original submission the company presented CDP12 and CDP24 outcomes for the intent-to-treat (ITT) analysis population and also for subgroups of patients with high activity (HA) disease and rapidly evolving severe (RES) disease, both for the direct comparison of OCR vs interferon β-1a (IFNβ-1a) in the OPERA trials and for the MTC analysis on a wider range of comparators.

2.1 Direct comparison

New data for CDP36 and CDP48 from the OPERA trials have been provided by the company in Table 1 in ACD response Appendix A. The hazard ratios for the pooled OPERA trials analysis suggest an overall 50% and 57% reduction in risk of progression based on CDP36 and CDP48 respectively, compared to 40% based on CDP12 and CDP24. The company concludes that ocrelizumab significantly reduces the risk of disability progression and this appears to be independent of the time period after which progression is confirmed. We agree that this conclusion appears reasonable. We note there are some limitations in these data, as follows, but they seem unlikely to invalidate the company's general conclusions:

- There is some variability between the OPERA trials: the CDP36 outcome was statistically significant in OPERA II but not in OPERA I;
- The analyses were post hoc (but risk of bias appears to be low);
- Only hazard ratios are reported, without the corresponding CDP estimates per trial arm (the ERG is therefore unable to check veracity of the results).

The CDP36 and CDP48 outcomes were not reported in any of the comparator trials and so these outcomes could not be investigated in MTC analyses.

2.2 MTC analyses

To address the sparsity of CDP24 values in their original submission, the company has updated their MTC analysis for the CDP24 outcome using two approaches to improve the estimation of confirmed disability progression. In Model 1 missing CDP24 values were imputed by using corresponding CDP12 values. Model 2 used a more complex analytical approach which jointly models the CDP12 and CDP24 outcomes.

General caveats

The new MTC analyses do not resolve the following limitations to the subgroup analyses for the HA and RES populations, which remain from the company's original MTC analyses reported in the CS:

- In order to form networks for the HA and RES subgroups the company included ITT data from trials of 'ABCR' (interferon β and glatiramer acetate) comparators, which requires an assumption that the treatment effect observed in the ITT population is the same as in the subgroups. The analyses using Model 1 and Model 2 require this assumption.
- Other potential limitations of the MTC subgroup analyses, not resolved by the Model 1 and Model 2 analyses, are: the subgroup analyses were not pre-specified; the subgroups were not randomised; and the MTC analysis of CDP24 and CDP12 assume proportional hazards. The company justified that the proportional hazards assumption appears appropriate for the OCR vs IFNβ-1a comparison in the OPERA trials, but they did not provide any justification in support of this assumption for other comparisons in the MTC analyses.

Due to the limitations of the subgroup MTC analyses, the company in their original submission urged caution in interpretation of the HA and RES subgroup analysis results and suggested that ITT analysis results should be considered alongside the subgroup analyses (CS section B.2.9.1). We note that the inclusion of ITT data in all subgroup networks means that there are no "pure" HA or RES subgroups in any of the presented MTC analyses.

Updated MTC analyses using Model 1 and Model 2

Model 1 is a simple imputation model in which missing values of CDP24 are replaced with the corresponding values of CDP12 from the same study. Model 2 is statistically more complex and accounts for the inter-relationship between the CDP12 and CDP24 outcomes by modelling the correlation structure of effectiveness estimates across outcomes and studies (i.e. accounting for both within-study and between-study correlations). Model 2 makes best use of the available CDP12 and CDP24 data (it can "borrow strength" across outcomes and studies[1]) and therefore should (in theory at least) provide more accurate and precise estimates of CDP24. As such, Model 2 would be the ERG's preferred approach for estimating CDP24 compared to Model 1. However, Model 2 requires that the correlation structure between effects and multiple outcomes is appropriately analysed, and that several key assumptions are satisfied. These assumptions include that the random effect is exchangeable across outcomes; and that outcomes are related but different in such a way

that there is no way of knowing the order of magnitude of effects on outcomes.[1] We have noted the following limitations in the way that the company has presented their analysis for Model 2:

- the company has not discussed any of the assumptions underlying the Model 2 approach and whether they were likely to be satisfied;
- the company based their analysis on an approach reported by Achana et al.[1] who found that the choice of prior distribution for the between-study covariance structure may influence the width of the credible intervals of model outputs;[1] however, the company has not provided sensitivity analyses on alternative priors or assumptions;
- the company has not specified whether a simplified analysis (common correlation assumption[1]) or a more complex analysis was performed;
- the company has not discussed statistical heterogeneity, or consistency for the Model 1 or Model 2 networks and has not discussed whether the number of studies available for the HA and RES subgroup networks would have been adequate for estimation of the between-study covariance matrix.

Despite these limitations in the reporting of the MTC analyses, the statistical code provided by the company and the Model 2 results provided in tables and forest plots together suggest that the overall modelling approach was likely to have been generally appropriate. The ERG's main concern is that the credible intervals reported for the CDP24 outcome from Model 2 may underestimate the uncertainty, due to lack of clarity around the specific analysis methods employed.

In conclusion, neither Model 1 nor Model 2 resolve the underlying limitations of the company's original MTC analyses, and we believe that uncertainty in the Model 2 results has not been adequately addressed. The new analyses of CDP24 provided by the company therefore do not appear to alter the company's existing conclusion (CS section B.2.9.1) that the disability progression results for the HA and RES subgroups should be interpreted with caution.

3 ERG analysis

The ERG checked the company's updated model and results for inconsistencies or errors, by replicating the changes made, working from the company's initial base case analysis. Our checks confirmed that, apart from testing the NICE committee's preferred assumptions, the updated model is consistent with the company's original model and the results reported in the company's appendix are correct. Below, we present selected scenario analyses to illustrate the cumulative effect of the new PAS for ocrelizumab (all comparators at list price) and the Committee's preferred assumptions. Tables of results are reproduced with PAS discounts for ocrelizumab and all comparators in a confidential addendum (Addendum 4 to the ERG report).

Results for the ITT population are summarised in Tables 2 to 9 below:

Table 1 **Original company base case** with the previous PAS for ocrelizumab and list price for all comparators.

Table 2 as in previous table, except for the addition of the new PAS discount for ocrelizumab

Table 3 as in previous table, except CDP12 outcome is replaced with an estimate of CDP24 from Model 1 (simple imputation, with missing CDP24 values replaced by CDP12).

Table 4 as in previous table with annual PML incidence 0.00028% for ocrelizumab (company estimate based on rate for rituximab in rheumatoid arthritis).

Table 5 **New company base case,** as in previous table with EDSS costs estimated from the UK MS Survey (updated to 2015/16 prices).

Table 6 New company base case with annual PML incidence of 2.1% for ocrelizumab, which is the rate modelled for natalizumab. This represents an upper limit to the impact of PML, as incidence is likely to be lower than this for ocrelizumab.

Table 7 New company base case with annual PML incidence of 1% for ocrelizumab

Table 8 New company base case with Model 2 estimate of CDP24 (joint estimation MTC, Achana et al. method)

Table 9 New company base case with Model 2 and 1% annual PML risk for ocrelizumab

We repeated these analyses for subgroups of patients with second-line highly active (HA) and Rapidly Evolving Severe (RES) MS. The company did not implement the Model 2 imputation for CDP24 for the subgroups. Due to uncertainty around the subgroup MTC results, we present additional scenario analyses around the new company base case results for HA and RES subgroups, by applying estimates of relative effects on CDP24 from the ITT Model 1 and Model 2 analyses.

In the tables below, we show Incremental Cost-Effectiveness Ratios (ICERs) based on full incremental analysis of ocrelizumab versus relevant comparators for each patient group:

- ITT population excludes natalizumab and fingolimod, which are not recommended for patients without HA or RES disease;
- HA includes alemtuzumab, ocrelizumab and fingolimod;
- RES includes alemtuzumab, ocrelizumab and natalizumab.

3.1 ITT population

Table 1 ITT: original company base case with previous ocrelizumab PAS

Technology	Costs (£)	QALYs	ICER (£ per QALY gained)	
			Incremental	Ocrelizumab vs. comparator
PegIFNB-1a	[redacted]	[redacted]	-	£35,028
Glatiramer acetate	[redacted]	[redacted]	Dominated	£27,304
IFNB-1b	[redacted]	[redacted]	Dominated	£23,711
IFNB-1a (Avonex)	[redacted]	[redacted]	Dominated	£22,841
IFNB-1a (Rebif)	[redacted]	[redacted]	Extendedly dominated	£25,911
Alemtuzumab	[redacted]	[redacted]	£13,289	Comparator dominates
Teriflunomide	[redacted]	[redacted]	Dominated	£9,832
Ocrelizumab	[redacted]	[redacted]	Dominated	-
Dimethyl fumarate	[redacted]	[redacted]	Dominated	OCR dominates

Table 2 ITT: original company base case with new ocrelizumab PAS

Technology	Costs (£)	QALYs	ICER (£ per QALY gained)	
			Incremental	Ocrelizumab vs. comparator
PegIFNB-1a	[redacted]	[redacted]	-	£27,492
Glatiramer acetate	[redacted]	[redacted]	Dominated	£20,918
IFNB-1b	[redacted]	[redacted]	Dominated	£17,373
IFNB-1a (Avonex)	[redacted]	[redacted]	Dominated	£16,687
IFNB-1a (Rebif)	[redacted]	[redacted]	Extendedly dominated	£18,255
Alemtuzumab	[redacted]	[redacted]	£13,289	Comparator dominates
Teriflunomide	[redacted]	[redacted]	Dominated	£2,401
Ocrelizumab	[redacted]	[redacted]	Dominated	-
Dimethyl fumarate	[redacted]	[redacted]	Dominated	OCR dominates

Table 3 ITT: previous table with Model 1 CDP24 (simple imputation)

Technology	Costs (£)	QALYs	ICER (£ per QALY gained)	
			Incremental	Ocrelizumab vs. comparator
PegIFNB-1a	[redacted]	[redacted]	-	£56,832
Glatiramer acetate	[redacted]	[redacted]	Dominated	£26,941
IFNB-1a (Avonex)	[redacted]	[redacted]	Dominated	£23,222
IFNB-1b	[redacted]	[redacted]	Dominated	£21,592
IFNB-1a (Rebif)	[redacted]	[redacted]	Dominated	£17,870
Alemtuzumab	[redacted]	[redacted]	£15,848	Comparator dominates
Teriflunomide	[redacted]	[redacted]	Dominated	£1,445
Ocrelizumab	[redacted]	[redacted]	Dominated	-
Dimethyl fumarate	[redacted]	[redacted]	Dominated	OCR dominates

Table 4 ITT: previous table with annual PML risk of 0.00028% for ocrelizumab

Technology	Costs (£)	QALYs	ICER (£ per QALY gained)	
			Incremental	Ocrelizumab vs. comparator
PegIFNB-1a	[redacted]	[redacted]	-	£56,833
Glatiramer acetate	[redacted]	[redacted]	Dominated	£26,941
IFNB-1a (Avonex)	[redacted]	[redacted]	Dominated	£23,222
IFNB-1b	[redacted]	[redacted]	Dominated	£21,592
IFNB-1a (Rebif)	[redacted]	[redacted]	Dominated	£17,870
Alemtuzumab	[redacted]	[redacted]	£15,848	Comparator dominates
Teriflunomide	[redacted]	[redacted]	Dominated	£1,446
Ocrelizumab	[redacted]	[redacted]	Dominated	-
Dimethyl fumarate	[redacted]	[redacted]	Dominated	OCR dominates

Table 5 ITT: previous table with UK MS Survey EDSS costs (new company base case)

Technology	Costs (£)	QALYs	ICER (£ per QALY gained)	
			Incremental	Ocrelizumab vs. comparator
PegIFNB-1a	[redacted]	[redacted]	-	£51,668
Glatiramer acetate	[redacted]	[redacted]	Dominated	£21,720
IFNB-1a (Avonex)	[redacted]	[redacted]	Dominated	£18,060
IFNB-1b	[redacted]	[redacted]	Dominated	£16,440
Alemtuzumab	[redacted]	[redacted]	£11,148	Comparator dominates
IFNB-1a (Rebif)	[redacted]	[redacted]	Dominated	£12,674
Ocrelizumab	[redacted]	[redacted]	Dominated	-
Teriflunomide	[redacted]	[redacted]	Dominated	OCR dominates
Dimethyl fumarate	[redacted]	[redacted]	Dominated	OCR dominates

Table 6 ITT: New company base case with 2.13% annual PML risk for ocrelizumab

Technology	Costs (£)	QALYs	ICER (£ per QALY gained)	
			Incremental	Ocrelizumab vs. comparator
PegIFNB-1a	[redacted]	[redacted]	-	£57,215
Glatiramer acetate	[redacted]	[redacted]	Dominated	£23,815
IFNB-1a (Avonex)	[redacted]	[redacted]	Dominated	£20,060
IFNB-1b	[redacted]	[redacted]	Dominated	£18,291
Alemtuzumab	[redacted]	[redacted]	£11,148	Comparator dominates
IFNB-1a (Rebif)	[redacted]	[redacted]	Dominated	£14,443
Ocrelizumab	[redacted]	[redacted]	Dominated	-
Teriflunomide	[redacted]	[redacted]	Dominated	OCR dominates
Dimethyl fumarate	[redacted]	[redacted]	Dominated	OCR dominates

Table 7 ITT: new company base case with 1% annual PML risk for ocrelizumab

Technology	Costs (£)	QALYs	ICER (£ per QALY gained)	
			Incremental	Ocrelizumab vs. comparator
PegIFNB-1a	[redacted]	[redacted]	-	£54,193
Glatiramer acetate	[redacted]	[redacted]	Dominated	£22,687
IFNB-1a (Avonex)	[redacted]	[redacted]	Dominated	£18,983
IFNB-1b	[redacted]	[redacted]	Dominated	£17,295
Alemtuzumab	[redacted]	[redacted]	£11,148	Comparator dominates
IFNB-1a (Rebif)	[redacted]	[redacted]	Dominated	£13,491
Ocrelizumab	[redacted]	[redacted]	Dominated	-
Teriflunomide	[redacted]	[redacted]	Dominated	OCR dominates
Dimethyl fumarate	[redacted]	[redacted]	Dominated	OCR dominates

Table 8 ITT: new company base case with Model 2 CDP24 (joint estimation)

Technology	Costs (£)	QALYs	ICER (£ per QALY gained)	
			Incremental	Ocrelizumab vs. comparator
PegIFNB-1a	[redacted]	[redacted]	-	£31,673
Glatiramer acetate	[redacted]	[redacted]	Dominated	£22,615
IFNB-1b	[redacted]	[redacted]	Dominated	£18,109
IFNB-1a (Avonex)	[redacted]	[redacted]	Dominated	£17,126
Alemtuzumab	[redacted]	[redacted]	£8,825	Comparator dominates
IFNB-1a (Rebif)	[redacted]	[redacted]	Dominated	£12,522
Ocrelizumab	[redacted]	[redacted]	Dominated	-
Teriflunomide	[redacted]	[redacted]	Dominated	OCR dominates
Dimethyl fumarate	[redacted]	[redacted]	Dominated	OCR dominates

Table 9 ITT: new company base case with Model 2 CDP24 and 1% annual PML risk with ocrelizumab

Technology	Costs (£)	QALYs	ICER (£ per QALY gained)	
			Incremental	Ocrelizumab vs. comparator
PegIFNB-1a	[redacted]	[redacted]	-	£33,050
Glatiramer acetate	[redacted]	[redacted]	Dominated	£23,620
IFNB-1b	[redacted]	[redacted]	Dominated	£19,037
IFNB-1a (Avonex)	[redacted]	[redacted]	Dominated	£18,006
Alemtuzumab	[redacted]	[redacted]	£8,825	Comparator dominates
IFNB-1a (Rebif)	[redacted]	[redacted]	Dominated	£13,330
Ocrelizumab	[redacted]	[redacted]	Dominated	-
Teriflunomide	[redacted]	[redacted]	Dominated	OCR dominates
Dimethyl fumarate	[redacted]	[redacted]	Dominated	OCR dominates

3.2 HA subgroup

Table 10 HA subgroup: original company base case with previous ocrelizumab PAS

Technology	Costs (£)	QALYs	ICER (£ per QALY gained)	
			Incremental	Ocrelizumab vs. comparator
Alemtuzumab	NA	NA	NA	NA
Ocrelizumab	[redacted]	[redacted]	-	-
Fingolimod	[redacted]	[redacted]	Dominated	OCR dominates

Table 11 HA subgroup: original company base case with new ocrelizumab PAS

Technology	Costs (£)	QALYs	ICER (£ per QALY gained)	
			Incremental	Ocrelizumab vs. comparator
Alemtuzumab	NA	NA	NA	NA
Ocrelizumab	[redacted]	[redacted]	-	-
Fingolimod	[redacted]	[redacted]	Dominated	OCR dominates

Table 12 HA subgroup: previous table with Model 1 CDP24 (simple imputation)

Technology	Costs (£)	QALYs	ICER (£ per QALY gained)	
			Incremental	Ocrelizumab vs. comparator
Alemtuzumab	[redacted]	[redacted]	-	Comparator dominates
Ocrelizumab	[redacted]	[redacted]	Dominated	-
Fingolimod	[redacted]	[redacted]	Dominated	OCR dominates

Table 13 HA subgroup: previous table with 0.00028% annual PML risk with ocrelizumab

Technology	Costs (£)	QALYs	ICER (£ per QALY gained)	
			Incremental	Ocrelizumab vs. comparator
Alemtuzumab	[redacted]	[redacted]	-	Comparator dominates
Ocrelizumab	[redacted]	[redacted]	Dominated	-
Fingolimod	[redacted]	[redacted]	Dominated	OCR dominates

Table 14 HA subgroup: previous table with UK MS Survey EDSS costs (new company base case)

Technology	Costs (£)	QALYs	ICER (£ per QALY gained)	
			Incremental	Ocrelizumab vs. comparator
Alemtuzumab	[redacted]	[redacted]	-	Comparator dominates
Ocrelizumab	[redacted]	[redacted]	Dominated	-
Fingolimod	[redacted]	[redacted]	Dominated	OCR dominates

Table 15 HA subgroup: new company base case with 2.13% annual PML risk for ocrelizumab

Technology	Costs (£)	QALYs	ICER (£ per QALY gained)	
			Incremental	Ocrelizumab vs. comparator
Alemtuzumab	[redacted]	[redacted]	-	Comparator dominates
Ocrelizumab	[redacted]	[redacted]	Dominated	-
Fingolimod	[redacted]	[redacted]	Dominated	OCR dominates

Table 16 HA subgroup: new company base case with 1% annual PML risk for ocrelizumab

Technology	Costs (£)	QALYs	ICER (£ per QALY gained)	
			Incremental	Ocrelizumab vs. comparator
Alemtuzumab	[redacted]	[redacted]	-	Comparator dominates
Ocrelizumab	[redacted]	[redacted]	Dominated	-
Fingolimod	[redacted]	[redacted]	Dominated	OCR dominates

Table 17 HA subgroup: New company base case with ITT Model 1 CDP24 estimates

Technology	Costs (£)	QALYs	ICER (£ per QALY gained)	
			Incremental	Ocrelizumab vs. comparator
Alemtuzumab	[redacted]	[redacted]	-	Comparator dominates
Ocrelizumab	[redacted]	[redacted]	Dominated	-
Fingolimod	[redacted]	[redacted]	Dominated	OCR dominates

Table 18 HA subgroup: New company base case with ITT Model 2 CDP24 estimates

Technology	Costs (£)	QALYs	ICER (£ per QALY gained)	
			Incremental	Ocrelizumab vs. comparator
Alemtuzumab	[redacted]	[redacted]	-	Comparator dominates
Ocrelizumab	[redacted]	[redacted]	Dominated	-
Fingolimod	[redacted]	[redacted]	Dominated	OCR dominates

Table 19 HA subgroup: new company base case with ITT Model 1 CDP24 estimates and 1% PML risk with ocrelizumab

Technology	Costs (£)	QALYs	ICER (£ per QALY gained)	
			Incremental	Ocrelizumab vs. comparator
Alemtuzumab	[redacted]	[redacted]	-	Comparator dominates
Ocrelizumab	[redacted]	[redacted]	Dominated	-
Fingolimod	[redacted]	[redacted]	Dominated	OCR dominates

Table 20: HA subgroup: new company base case with ITT Model 2 CDP24 estimates and 1% PML risk with ocrelizumab

Technology	Costs (£)	QALYs	ICER (£ per QALY gained)	
			Incremental	Ocrelizumab vs. comparator
Alemtuzumab	[redacted]	[redacted]	-	Comparator dominates
Ocrelizumab	[redacted]	[redacted]	Dominated	-
Fingolimod	[redacted]	[redacted]	Dominated	OCR dominates

3.3 RES subgroup

Table 21 RES subgroup: Company original base case with previous ocrelizumab PAS

Technology	Costs (£)	QALYs	ICER (£ per QALY gained)	
			Incremental	Ocrelizumab vs. comparator
Alemtuzumab	NA	NA	NA	NA
Ocrelizumab	[redacted]	[redacted]	-	-
Natalizumab	[redacted]	[redacted]	£1,065,854	£1,065,854 SW

Table 22 RES subgroup: Company original base case with new ocrelizumab PAS

Technology	Costs (£)	QALYs	ICER (£ per QALY gained)	
			Incremental	Ocrelizumab vs. comparator
Alemtuzumab	NA	NA	NA	NA
Ocrelizumab	[redacted]	[redacted]	-	-
Natalizumab	[redacted]	[redacted]	£1,226,646	£1,226,646 SW

Table 23 RES subgroup: previous table with Model 1 CDP24 estimates (simple imputation)

Technology	Costs (£)	QALYs	ICER (£ per QALY gained)	
			Incremental	Ocrelizumab vs. comparator
Alemtuzumab	[redacted]	[redacted]	-	Comparator dominates
Ocrelizumab	[redacted]	[redacted]	Dominated	-
Natalizumab	[redacted]	[redacted]	£2,105,445	£129,304 SW

Table 24 RES subgroup: previous table with 0.00028% annual PML risk with ocrelizumab

Technology	Costs (£)	QALYs	ICER (£ per QALY gained)	
			Incremental	Ocrelizumab vs. comparator
Alemtuzumab	[redacted]	[redacted]	-	Comparator dominates
Ocrelizumab	[redacted]	[redacted]	Dominated	-
Natalizumab	[redacted]	[redacted]	£2,105,445	£129,302 SW

Table 25 RES subgroup: previous table with UK MS Survey EDSS costs (new company base case)

Technology	Costs (£)	QALYs	ICER (£ per QALY gained)	
			Incremental	Ocrelizumab vs. comparator
Alemtuzumab	[redacted]	[redacted]	-	Comparator dominates
Ocrelizumab	[redacted]	[redacted]	Dominated	-
Natalizumab	[redacted]	[redacted]	£2,091,517	£124,078 SW

Table 26 RES subgroup: New company base with 2.13% annual PML risk for ocrelizumab

Technology	Costs (£)	QALYs	ICER (£ per QALY gained)	
			Incremental	Ocrelizumab vs. comparator
Alemtuzumab	[redacted]	[redacted]	-	Comparator dominates
Ocrelizumab	[redacted]	[redacted]	Dominated	-
Natalizumab	[redacted]	[redacted]	£2,091,517	£114,143 SW

Table 27 RES subgroup: New company base case with 1% annual PML risk for ocrelizumab

Technology	Costs (£)	QALYs	ICER (£ per QALY gained)	
			Incremental	Ocrelizumab vs. comparator
Alemtuzumab	[redacted]	[redacted]	-	Comparator dominates
Ocrelizumab	[redacted]	[redacted]	Dominated	-
Natalizumab	[redacted]	[redacted]	£2,091,517	£119,262 SW

Table 28 RES subgroup: New company base case with ITT Model 1 CDP24

Technology	Costs (£)	QALYs	ICER (£ per QALY gained)	
			Incremental	Ocrelizumab vs. comparator
Alemtuzumab	[redacted]	[redacted]	-	Comparator dominates
Ocrelizumab	[redacted]	[redacted]	Dominated	-
Natalizumab	[redacted]	[redacted]	Dominated	£384,422 SW

Table 29 RES subgroup: New company base case with ITT Model 2 CDP24 estimates

Technology	Costs (£)	QALYs	ICER (£ per QALY gained)	
			Incremental	Ocrelizumab vs. comparator
Alemtuzumab	[redacted]	[redacted]	-	Comparator dominates
Ocrelizumab	[redacted]	[redacted]	Dominated	-
Natalizumab	[redacted]	[redacted]	Dominated	OCR dominates

Table 30 RES subgroup: New company base case with ITT Model 1 CDP24 estimates and 1% annual PML risk with ocrelizumab

Technology	Costs (£)	QALYs	ICER (£ per QALY gained)	
			Incremental	Ocrelizumab vs. comparator
Alemtuzumab	[redacted]	[redacted]	-	Comparator dominates
Ocrelizumab	[redacted]	[redacted]	Dominated	-
Natalizumab	[redacted]	[redacted]	Dominated	£349,027 SW

Table 31 RES subgroup: New company base case with ITT Model 2 CDP24 and 1% annual PML risk with ocrelizumab

Technology	Costs (£)	QALYs	ICER (£ per QALY gained)	
			Incremental	Ocrelizumab vs. comparator
Alemtuzumab	[redacted]	[redacted]	-	Comparator dominates
Ocrelizumab	[redacted]	[redacted]	Dominated	-
Natalizumab	[redacted]	[redacted]	Dominated	£19,200,393 SW

4 References

1. Achana FA, Cooper NJ, Bujkiewicz S, Hubbard SJ, Kendrick D, Jones DR. Network meta-analysis of multiple outcome measures accounting for borrowing of information across outcomes. BMC Med Res Methodol 2014; 14: 92 (16 pp).