



# Oral and Monoclonal Antibody Treatments for Relapsing Forms of Multiple Sclerosis

Response to Public Comments on Draft Evidence Report

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#	Comment	Response/Integration
<b>Manufacturers</b>		
<b>Biogen</b>		
1.	<p><b>Each DMT has an individual efficacy and safety profile.</b></p> <p>As already highlighted in prior comments to this class assessment, MS is a very complex autoimmune disease and with multiple DMTs that have different MOAs. Specificities of each DMT and their associated mechanisms of action are currently not sufficiently characterized or acknowledged in the draft evidence report: the MABs are being treated as if they are mechanistically the same, rather than a type of molecule. There appears to be a lumping of efficacy and safety of all MABs, rather than by specificity of each MAB, each unique target epitope and thereby unique MOA. This draft often states characteristics of anti-CD20s under ‘MAB’ classification and inadvertently not acknowledging the MOA of natalizumab is differentiated and non-immune cell depleting. We strongly suggest using ‘high efficacy therapies (HET)’ in place of ‘MABs’ when referencing the overall high efficacy therapeutic options.</p>	<p>We clarified our use of “monoclonal antibodies” throughout the report to acknowledge potential differences in mechanism of action amongst the drugs. The HET term encompasses more DMTs than those included in our report and there may be differing definitions (e.g., many experts classify S1P receptor inhibitors as HET; however, in our review they are classified in the oral DMT category), so to maintain specificity we have used “monoclonal antibodies” as a designation for this group of drugs.</p>
2.	<p><b>Reported drug costs are inconsistent across DMTs and could lead to non-informative conclusions.</b></p> <p>While the reported net price for ocrelizumab is derived from data submitted directly from the manufacturer, the net prices for natalizumab and ofatumumab are estimated from SSR Health, LLC. The methodology used by SSR Health, LLC is not clearly defined and may not reflect the real-world costs of these DMTs paid by various plans. The net price of ublituximab is assumed to be equivalent to the net price of ocrelizumab, which also may not be an accurate reflection of its net price in a real-world setting. Comparing net prices of DMTs with different routes of administration (e.g., subcutaneous vs intravenous) is challenging due to differing requirements surrounding the utilization, management, reimbursement of these products. Lastly, it is unclear whether payer net price or gross-to-net is used for the analyses.</p> <p>We recommend that ICER apply a consistent approach for estimating net price across all DMTs in the budget impact and cost effectiveness analyses to improve comparability of the results. If such an approach is not feasible with the available information, ICER should indicate this as a limitation of all analyses that utilize net price to enable a fairer interpretation of results. Comparing one product at a manufacturer-stated price to other DMTs at different prices based on assumptions may lead to inaccurate interpretation of the results.</p>	<p>Our approach to estimating drug acquisition costs for the economic model follows the <a href="#">ICER Reference Case</a>. All manufacturers had the opportunity to provide net prices through the data request stage of this review. Following feedback we received after the model analysis plan was posted, we used WAC plus SSR Health for all treatments (provider-administered and not provider-administered) that had a price and where the manufacturer didn’t provide a net price, to further promote consistency and given the starting age of the cohort. We explicitly state in numerous places that the price for ublituximab is a placeholder price.</p>
3.	<p>Additionally, in the draft report monitoring resource utilization associated with each intervention hasn’t been described. In reviewing the economic model, it is apparent</p>	<p>Please refer to Table E15 and Table E17 in the supplement for a list of the monitoring requirements and monitoring costs included in the model. Monitoring requirements that</p>

	<p>that ICER didn't include any monitoring cost associated with anti-CD20s. In the US prescribing information (USPI) it states there are assessments needed prior to first dose, monitoring for the levels of quantitative serum immunoglobulins during and after treatment and monitoring for PML including MRI and Biogen recommend to carefully reflect such monitoring costs in the economic evaluation to ensure a balanced comparison between interventions.</p>	<p>occurred prior to the first dose and would have occurred in both the intervention and comparator trace were not modeled.</p>
<p>4.</p>	<p><b>Quality of Life of patients on EDSS 8.0 to 9.5.</b></p> <p>For the disease states EDSS 8.0 to 9.5, an extrapolation has been used which extends published values used for the states EDSS 0 to 7.5. The rationale given for this is that such dramatic reductions in utility values are not in line with other published literature. The largest burden of illness study conducted to date in MS included approximately 17,000 people with MS across 16 different countries in Europe. Utility estimates were derived from patient responses to the EQ-5D survey as part of this study, and in each of the 16 countries included in the study, the quality of life was negative for patients in EDSS &gt;9.0, which reflects the severity of this disease and the extremely poor quality of life of these people and consequent burden to their caregivers.</p> <p>ICER's methodology is not a patient-centered rationale; there is no fundamental reason to expect that utility values should be smoothly dependent on disease stage, given the nonlinear and complex ways in which progression affects function and life of people living with MS. We do not believe that a statistical extrapolation can better capture the quality-of-life changes than the underlying data itself does and serves only to increase structural and unknown uncertainty in the model results. For this reason, we recommend the use of the unadjusted, observed utility values in preference to the extrapolation in the base case.</p>	<p>We did not assume a linear relationship of EDSS with utility. As explained in the report and after conversations with MS economic experts, we fit a utility function based on EDSS and EDSS<sup>2</sup>.</p> <p>Our rationale is patient-centered in that we do not believe that people with an EDSS greater than 7 have a worse quality of life than someone who is dead. This was informed by conversations had with patients.</p>
<p>5.</p>	<p><b>Choice of comparator and discontinuation pattern in the cost-effectiveness model do not provide information applicable in clinical practice.</b></p> <p>The chosen interventions in the analysis, natalizumab, rituximab, ofatumumab, ocrelizumab and ublituximab, are generally considered high-efficacy therapies and predominately used for patients exhibiting a high level of disease activity; however, the comparator used, DMF, is an oral treatment that is generally considered a moderate-efficacy therapy and used primarily for patients with mild to moderate disease activity. Therefore, comparing DMF to these high-efficacy DMTs may be a comparison with limited clinical relevance in real-world use of DMTs. We suggest that ICER acknowledges that this comparison may have limited clinical application because DMF may not be the treatment of choice for people with highly active disease.</p>	<p>Dimethyl fumarate was selected as the comparator following numerous conversations with stakeholders suggesting it was an effective market leader. Choosing a comparator with higher efficacy and lower discontinuation than dimethyl fumarate would have made the monoclonal antibodies look worse clinically.</p>
<p>6.</p>	<p>Furthermore, the inclusion of rituximab is not appropriate. It is neither approved nor projected to be approved by the</p>	<p>Our review of the literature suggests that rituximab is used for the treatment of MS both in the United States and</p>

	<p>FDA or any regulatory agency for the use in patients with RRMS. We strongly object to the inclusion of rituximab in any indirect treatment comparison for RRMS.</p>	<p>abroad, and clinical experts and patient groups confirmed that rituximab is an important part of the treatment arsenal, even if it doesn't have a label for MS treatment. Given new data that has emerged regarding the efficacy of rituximab, we feel that it is important to include rituximab in our report to ensure that stakeholders are able to assess the value of rituximab treatment alongside other commonly used DMTs.</p>
7.	<p>Lastly, in the model, patients who discontinue initial therapy transition to a therapy with characteristics similar to that of the "market leading antibody." This can make the results more complicated to interpret for real-world decision making for the following reasons: (1) The "market leading monoclonal antibody" has different discontinuation rates if used as an initial therapy than as a follow-up (where no discontinuation is assumed); the assumption of no discontinuation due to patient tolerance is particularly strong over a lifetime time-horizon. (2) It is unrealistic for all patients to discontinue to the "market-leading antibody," particularly those who used that same antibody in first-line therapy. (3) The absolute efficacy estimates are strongly driven by the efficacy estimate of the follow-up therapy, particularly as discontinuation rates for the initial therapy rise.</p> <p>We would therefore recommend using a "blended" basket for the follow-up therapy. This would take the form of a weighted average of cost and efficacies over all the modelled antibody therapies, with an appropriate rate of subsequent discontinuation to no treatment from this basket. This new approach would offer both more realism as well as a more conservative estimate of long-term outcomes and costs.</p>	<p>We agree that the specific subsequent treatment will vary in the real world; however, our objective is not to recommend treatment sequences or evaluate the cost effectiveness of a specific treatment sequence. To achieve the objective of our analysis of estimating the cost effectiveness of a specific intervention, we held this subsequent treatment fixed to emphasize the potential differences in the initial treatment. Our approach standardized the treatment switch across the modeled arms (both the intervention and the comparator) and ensured the cost and effectiveness of the subsequent treatment did not drive the results. The subsequent treatment characteristics were varied in scenario analyses, and as can be observed by reviewing the results of the scenario analyses, so long as the subsequent treatment is consistent across the intervention and comparator, the subsequent treatment influences the findings very little. Rather the initial treatment drives the findings, which aligns with our intended objective.</p>
8.	<p><b>The Draft Evidence Report Excludes Important Published Data on Patient-Relevant Outcomes and only partially recognizes the holistic societal implications of MS.</b></p> <p>The proposed selection of studies only includes publications that either reported relapse rates or sustained disability progression. This leaves an appreciable gap to many important publications on quality of life, brain atrophy, cognitive outcomes, upper limb functionality, and other secondary, tertiary, sub-group and ad-hoc outcomes which are typically reported in additional publications following the main clinical trial publication. We believe that patient reported outcomes are important in treatment decisions and should be incorporated in an assessment of comparative effectiveness. We request that these factors be acknowledged as a study limitation.</p> <p>Additional limitations to this analysis include lack of an accounting for DMT impact on multiple measurable symptoms, longitudinal benefits experienced over time on DMT, and potential changes to comorbid conditions and associated concomitant medications. All measurable</p>	<p>We agree that there are many patient-important outcomes in assessing the impact of DMTs on MS. In our conversations with patients and clinical experts, relapse rates and disability progression were both identified as important and relevant considerations when selecting a DMT. We identified several factors that precluded us from assessing comparative effectiveness on additional outcomes including incomplete reporting, differing intervals of follow-up, and the evolution of diagnostic tools across more than 30 years of MS trials, and we have acknowledged these limitations in the report. Thus, our focus in the report is on the ARR and CDP outcomes for comparisons across DMTs. We have included some assessment of subgroup data in the supplement (see Section D6), and have also amended the report to discuss that there may be other outcomes we did not include in our assessment.</p> <p>Additionally, in our model, progression is based on EDSS scores. Although the measurement of EDSS has limitations, symptoms are correlated with EDSS and thus would be indirectly included in our value assessment to the extent that a treatment delayed EDSS progression.</p>

	<p>symptoms are not assessed for value analysis; some with proven significant improvement for patients. For example, sexual dysfunction, depression, fatigue, bladder and bowel control have all been areas of significant improvement with, for example, natalizumab.</p>	
9.	<p><b>Specific issues and recommendations (in order of appearance).</b></p> <p>Background, Page 3: Table 1.1 is not accurate for MOA for Tecfidera (DMF) and Vumerity (DRF). They are noted as ‘anti-oxidative’. Anti-oxidative is a result of the primary MOA with Nrf2 modulation (as well as other distinct mechanistic pathways). Nuclear factor (erythroid-derived 2)-like 2 (Nrf2) is a key transcription factor controlling many aspects of cell homeostasis in response to oxidative and toxic insults. Importantly, Nrf2 has the potential to reduce numbers of overactive microglia and astrocytes, which are thought to make substantial contributors to CNS pathology. DMF, but not monomethyl fumarate (MMF), have Nrf2-independent MOA as well. DMF, but not MMF, inhibit nuclear factor kappa B (NF-κB) activity in vitro and inhibits T-cell activation in vitro in an Nrf2-independent mechanism. Moreover, DMF, but not MMF, blocks the expression of proinflammatory cytokine interferon-alpha. We recommend editing the table lines for Tecfidera and Vumerity to read ‘Nrf2 activator and NF-κB inhibitor’, rather than ‘anti-oxidative’; no such change is needed for Bafiertam (MMF).</p>	<p>Thank you for the correction. Table 1.1 has been revised.</p>
10.	<p>Indirect Evidence: Ublituximab versus Other DMTs and Placebo, page 8: The current sentence ‘Diroximel fumarate and monomethyl fumarate are active metabolites of dimethyl fumarate’ is scientifically inaccurate and should be revised. We suggest replacing by the following statement: Enzymatic hydrolysis of both dimethyl fumarate and diroximel fumarate results in the active metabolite monomethyl fumarate.</p>	<p>Thank you for the correction. This sentence has been revised.</p>
11.	<p>Harms of Monoclonal Antibody DMTs, Page 16: The draft safety data could benefit from additional information. Other infections, beyond PML, associated with other high efficacy treatments, are not recognized. Additionally, anti-CD20 therapies have warnings associated with reduction in immunoglobulins. These therapies also have warnings for infants born to mothers taking these treatments in that the inadvertent infant B-cell depletion must be monitored and replenished before any live or live-attenuated vaccinations can be given. We respectfully request that such information be included and associated monitoring costs should be accurately captured in the cost-effectiveness model as well.</p>	<p>The Harms section has been updated to include the risk of hypogammaglobulinemia and its impact on live-vaccine administration.</p> <p>Please refer to Table E15 and Table E17 in the supplement for a list of the monitoring requirements and monitoring costs included in the model. Monitoring requirements that occurred prior to the first dose and would have occurred in both the intervention and comparator trace were not modeled.</p>
12.	<p>Harms of Monoclonal Antibody DMTs, Page 16: The statement “Cases of PML are rare and are associated with three risk factors: prior use of immunosuppressants, more than 24 months of natalizumab exposure, and presence of anti-JCV antibodies” is not relevant for other MS DMTs. These risk factors have been determined and established in natalizumab-treated patients only. We recommend revising to “Cases of natalizumab-related PML are rare and are</p>	<p>This sentence has been revised to reflect that the three risk factors are relevant only for natalizumab.</p>

	associated with three risk factors: presence of anti-JCV antibodies, longer treatment duration, especially beyond 2 years, and prior treatment of immunosuppressants.” As per the Tysabri® USPI.	
13.	Harms of Monoclonal Antibody DMTs, Page 16: The statement “The risk of developing PML can be mitigated by testing for JCV in patients on higher-risk drugs” is applicable only to Biogen’s natalizumab (Tysabri) treated patients. The anti-JCV antibody test should only be used for patients considering or taking Tysabri. This test is validated only for Tysabri; it is not validated for any other MS therapy. Tysabri’s JCV test/PML risk stratification is unique to Biogen’s natalizumab alone and should not be used for any other treatment. This point is critical to correct as it can lead to mitigation strategies for PML for other MS DMTs that are inappropriate and could potentially harm patients. Other DMTs; rituximab, fingolimod, ocrelizumab all do not have mitigation strategies for the risk of PML. We recommend revising to “The risk of developing natalizumab-related PML can be mitigated by testing for JCV in patients only on Biogen’s natalizumab”.	This sentence has been revised to reflect that monitoring with JCV testing is specific to natalizumab.
14.	Harms of Monoclonal Antibody DMTs, Page 16: The statement “Discontinuation of natalizumab is associated with increased risk of rebound relapse rates” should be reviewed. While there may always be outliers, the return of disease activity of patients treated with natalizumab has been examined in multiple studies. The studies have shown that there was a return of disease activity similar to what was seen before natalizumab treatment when not appropriately transitioned onto another DMT.	We appreciate the references provided regarding natalizumab rebound relapse rates. This statement has been revised to reflect that there are heterogenous findings in the literature on this topic. Our statement is also a reflection of a systematic review and meta-analysis (Prosperini 2019 et al.), which identified several patient characteristics associated with an increased risk of post-natalizumab disease reactivation (O’Connor 2011 et al. and Hartung 2021 et al.).
15.	Harms of Monoclonal Antibody DMTs, page 16: We strongly disagree with the statement “Limited observational data on the use of monoclonal antibody DMTs (natalizumab, ofatumumab, ocrelizumab) prior to conception or during pregnancy suggests no increased risk of adverse outcomes”. For these DMTs, the currently approved prescribing information state that there are currently no adequate data on the developmental risk associated with use of these DMTs in pregnant woman. <sup>2,3,15</sup> Observational studies do not provide enough information which would allow a claim of “no increased risk”. We recommend rewriting this statement as suggested above.	This statement was revised to reflect that there is insufficient high-quality evidence to assess monoclonal antibody DMTs and their impact on pregnancy-related outcomes.
16.	Heterogeneity, page 19: Within the Subgroup Analysis and Heterogeneity, we recommend that duration of disease is discussed in this section. This is relevant for the older studies that are included in the analysis. AFFIRM enrolled patients who had not received any prior DMT for at least the previous 6 months; approximately 94% were treatment naïve. Median age was 37, with a median disease duration of 5 years. In more recent trials, more patients have been treated with prior DMT, and disease duration was either similar or decreased, which can mean that patients were treated soon after diagnosis. Conversely, in AFFIRM patients might have not been placed on therapy right after MS	Thank you for your comment. We have updated the Heterogeneity section to include duration of disease as a potential source of heterogeneity. However, we don’t have any data to suggest this actually impacts the intervention’s effect. Furthermore, we are unaware of evidence that shows placebo response has uniformly changed over the time period reflected in these studies. For example, the AFFIRM trial was considered to be similar to the other trials of the interventions in our review in terms of age, the form of MS, baseline EDSS score, and the average number of relapses in the previous 12 months.



	<p>diagnosis. This would significantly affect heterogeneity of the populations and potentially the disability outcomes for these populations. Recent studies have shown that treatment with DMTs soon after diagnosis leads to decreased disability over time compared to patients that delay the start of a DMT. Also, it was mentioned in the NMA limitations of the CDP included in the Appendix of the report was "we had to introduce older trials." Older trials PRISMS (1998) and BRAVO (2014). The AFFIRM pivotal trial manuscript was published in 2006. Therefore, we recommend mentioning this as a limitation to the analysis.</p>	<p>We specifically mentioned PRISMS and BRAVO trials because these were interferon trials that were not part of the interventions being considered in our review but had to be introduced to complete our network. We conducted a sensitivity analysis where we excluded both trials (PRISMS and BRAVO) from our analysis. The exclusion of these trials did not change the result for any interventions we could evaluate without these trials.</p>
17.	<p>3.3. Summary and Comment, page 23: "Short-term safety signals appear similar across the drugs, barring a black box warning of an elevated risk of PML with natalizumab, but there is no long-term safety data for ublituximab yet." We recommend revising to include that rituximab also has a black box warning for PML, "Short-term safety signals appear similar across the drugs, barring a black box warning of an elevated risk of PML with natalizumab and rituximab, but there is not long-term safety data for ublituximab yet."</p>	<p>This sentence has been revised.</p>
18.	<p>Assessment of Bias, page D11 and D3 Evidence Tables, page D27: We kindly request a change to both Table D8. Study Design and Table D4. Risk of Bias Assessment, regarding the CONFIRM study design description and 'randomization concerns', respectively. Both DEFINE and CONFIRM were randomized, double-blind, placebo-controlled, Phase 3 clinical trials. CONFIRM in addition to the placebo arm, did have a rater-blinded, active agent (glatiramer acetate) included as a reference comparator to allow a relative benefit-risk assessment of DMF through comparison to the active-treatment groups with the placebo group. As these studies were nearly identical in design, their designation should both read 'low' on this table.</p>	<p>Table D4 was edited for the CONFIRM study to reflect that there was low risk of bias arising from the randomization process.</p> <p>Table D8 was edited for the CONFIRM study to reflect that it was a randomized, double blind (GA arm was rater-blinded), and placebo-controlled study.</p>
<b>Bristol Myers Squibb</b>		
1.	<p>BMS appreciates that clinically important outcomes have not routinely and/or consistently been reported in all clinical trials of MS treatments. As such, it may not be possible to include these measures, as well as novel endpoints, within the framework of an NMA. However, BMS recommends that ICER consider additional methods and sources of evidence for these outcomes. For example, matching-adjusted indirect comparison (MAIC), which typically allows for the evaluation of all reported endpoints and can also address cross-trial patient-level heterogeneity, has been used to evaluate the relative value of disease modifying therapies for the treatment of relapsing forms of MS. Although NMAs are a robust method to conduct indirect treatment comparisons (ITCs), alternative ITC methods, such as MAIC, can be used to generate additional comparative evidence for endpoints of interest, including fatigue, cognition, brain volume loss, annualized relapse rates, CDP, etc. In fact, MAICs have two main advantages compared to standard NMAs. First, MAICs typically allow for more endpoints to be compared between two treatments of interest such that,</p>	<p>The advantages of MAIC are well noted. However, as you know, the first consideration in assessing the feasibility of MAIC is the availability of patient-level data on at least one of the treatments compared, and ICER does not have access to patient-level data. Therefore, MAIC is only possible when initiated by the manufacturer of the treatments being compared. Further, NMA, which is the gold standard for indirect comparisons, has the advantage that it can incorporate all relevant treatments in the analyses by combining direct and indirect evidence within a network, thus reflecting the totality of available evidence. In contrast, MAICs produce only pairwise comparisons. Finally, although we could only conduct NMAs for the outcomes that were sufficiently similar in terms of definition, timepoint, and other relevant characteristics, the other patient-important outcomes are described qualitatively in the report.</p>

	<p>even when outcomes are defined differently across trials, the availability of patient-level data provides opportunities for outcomes in one trial to be redefined to match the definitions in the comparator trial. Second, MAICs allow for the adjustment of multiple cross trial differences in patient characteristics that are expected to impact the outcomes of interest, and these adjustments may result in relative treatment effects estimates that differ substantially from the ones non-adjusted ITCs yield. While these adjustments are technically possible in the NMA framework, they are rarely feasible in practice.</p> <p>MAICs, and other ITC approaches, can also be used to comparatively evaluate long-term safety data collected in trial extension studies to provide a more balanced and complete understanding of the risk-benefit profiles of these therapies. In their assessment, ICER could also consider complementing clinical evidence with real-world evidence of the relative benefits of these treatments in terms of key outcomes of interest.</p> <p>Technical challenges in the assessment conducted by ICER precluded the consideration of important clinical outcomes such as fatigue, cognition, and brain volume preservation. To address these challenges, alternative data sources and methods should be considered to allow for a more comprehensive evaluation of the relative value of the treatments for MS.</p>	
<b>Genentech</b>		
1.	<p>We recognize the challenges of conducting an assessment of comparative effectiveness and cost-effectiveness in a heterogeneous and evolving disease area with many treatment options, limited head-to-head trial data, and variability in clinical experience and availability of real-world data. We advise ICER to take a more holistic perspective on the available evidence – including the full scope of trial data as well as real-world evidence – to account for the clinical understanding that is gained and additional benefits that have been demonstrated for products like Ocrevus with significant time on market.</p>	<p>We appreciate that there are many sources of data for MS treatment, including real-world evidence. We have included real-world evidence where appropriate in our report (for example, for the long-term harms of DMTs and also in the economic model). Since the main focus of our report is to compare outcomes across agents, we are limited to the ARR and CDP outcomes, as other secondary, tertiary, and exploratory outcomes were not consistently measured across trials.</p>
2.	<p><b>Recommendation:</b> Review and reconcile inconsistencies in the conclusions regarding ublituximab’s NHB with findings for both ARR and CDP from the NMA, as well as ICER’s previous reviews of investigational therapies.</p> <p><b>Rationale:</b> In ICER’s assessment of the comparative clinical effectiveness of MS therapies, the results of the NMA suggest that ublituximab does not achieve a statistically significant treatment effect on either 3-month or 6-month CDP relative to placebo (Figures 3.2 and 3.3). However, on page ES2, ICER states that “ublituximab showed superior net health benefit compared with no DMT” and on pages 23-24, ICER concludes “ublituximab produced statistically significant improvements in ARR and CDP compared with no</p>	<p>Thank you for noting these inconsistencies. We have edited the language to more accurately reflect our NMA findings. While we acknowledge that the CDP outcome compared with placebo did not reach statistical significance, the hazard ratio was in line with other monoclonal antibodies (ofatumumab, natalizumab) and neared statistical significance (the 95% CI just crossed 1). In addition, the fact that ublituximab showed improvement in secondary outcomes in the ULTIMATE I and II trials, has a mechanism of action similar to some of the other monoclonal antibodies, and that treatment with any DMT clearly slows progression of disease adds to our certainty that treatment with ublituximab would likely have a substantial net health benefit over no treatment, which corresponds to the “A” rating given in the report.</p>



	<p>DMT. Given the progressive nature of MS and the high likelihood of disability with no DMT treatment, even with the risk of adverse events with active treatment, we judge that there is high certainty of a substantial net health benefit of ublituximab compared with no DMT (A) [superior].”</p> <p>Ublituximab, along with all therapies reviewed, achieved statistical significance on ARR relative to placebo (Figure 3.1). As ARR is the primary endpoint for most Phase 3 trials in relapsing MS, it is reasonable that treatment effect on ARR contributes to the NHB rating. However, the NHB rating (and the supporting text on pages ES2 and 23-24) should also appropriately reflect ublituximab’s lack of significant impact on CDP, particularly because, as ICER notes, patients and clinicians identify prevention/slowing of disability as the most important outcome.</p> <p>Furthermore, ICER’s previous reviews of MS therapies and assessment of NHB have additionally considered the availability of real-world data to assess uncommon serious AEs and to corroborate findings of clinical trials given the limited number of patients and short follow-up among those patients treated with an investigational therapy . Previous reviews have also acknowledged the uncertainty until FDA approval, which includes an independent review of the full clinical trial data to assess the balance of benefits and risks. These considerations are lacking in the clinical value assessment of ublituximab, and should be revisited to increase the objectivity and consistency of ICER’s assessments.</p> <p>Implications: Conclusions about superior NHB, as written in the Draft Evidence Report, may be misleading, as they do not holistically reflect ublituximab’s performance in the NMA or capture broader considerations about the breadth of evidence available for ublituximab. Given the importance of the disability progression outcome, independent assessment of benefit-risk by the FDA, and long-term safety and effectiveness data for PwMS, their families, and the health system, it is critical that ICER presents a more comprehensive assessment of ublituximab’s NHB.</p>	
3.	<p>Recommendation: Remove the hypothetical biosimilar scenario analysis from the economic assessment, and focus the review on FDA-approved or soon to be approved treatments for relapsing forms of MS.</p> <p>Rationale: The scenario analysis comparing the interventions to a hypothetical biosimilar lacks precedent, is not grounded in evidence, and may risk encouraging off-label use of treatments which have not been adequately studied in MS, are not FDA approved, and thus present unknown benefits and risks.</p>	<p>The hypothetical biosimilar comparator is not our base case, doesn’t factor into our health-benefit price benchmarks, and is only presented as a scenario analysis. There are MS monoclonal antibody biosimilars (not rituximab) in the pipeline and as such, there is policy relevance to this scenario. A placeholder price for this potential biosimilar comparator was based on the price of biosimilar rituximab, which is another biosimilar monoclonal antibody.</p> <p>Another important risk to people with MS and all patients is charging prices that do more harm than good. The evidence suggests all modeled monoclonal antibody treatments, including ocrelizumab, are priced higher than the health benefits and any cost savings they confer when compared to</p>

<p>In this hypothetical scenario, ICER assumes the biosimilar has effectiveness equal to the average treatment effectiveness of the modeled interventions and cost equivalent to the average sales price for biosimilar rituximab. These assumptions create the impression that the hypothetical treatment is a proxy for biosimilar rituximab, which may cause readers to infer that the assumed effectiveness of the ‘hypothetical’ biosimilar in the CEA is evidence-based, potentially supporting off-label use of rituximab in MS. On the contrary, as noted in Genentech’s previous recommendations to ICER related to this review, there is limited data to support the off-label use of rituximab in this space. In the Draft Evidence Report, ICER acknowledges the lack of high-quality evidence for rituximab’s impact on disability progression. Furthermore, in a recently published comparative effectiveness study of rituximab vs. ocrelizumab, the evidence failed to demonstrate that rituximab is non-inferior to ocrelizumab in a population of RRMS patients, and rituximab-treated patients experienced significantly higher ARRs (rate ratio 1.8 (95% CI 1.4-2.4), p&lt;0.01) compared with ocrelizumab [4].</p> <p>Based on ICER’s 2022-2023 Value Assessment Framework as well as the growing body of past ICER assessments, there is no precedent to include comparisons of interventions to a ‘hypothetical’ comparator. The methods and rationale for use of a ‘hypothetical’ comparator in this review are also absent from acknowledged best practices for health economic modeling. Consequently, the proposed scenario analysis will fail to meet the goals of HTA, which are to generate relevant evidence and inform key decision-makers about the dissemination, use, and reimbursement of available health technologies based on currently available or soon to be available real-world treatment choices.</p> <p>Implications: This scenario analysis could encourage use of off-label products that lack robust clinical evidence or formal assessment of benefit-risk. Any impact to access based on these findings may put PwMS at risk by encouraging use of a treatment without well-studied safety and efficacy in MS.</p>	<p>generically available dimethyl fumarate. We should all work toward policy solutions that incentivize fair pricing and fair access. Finally, our health-benefit price benchmark range for on-label monoclonal antibody DMTs is higher than that of rituximab’s annualized price suggesting a counter argument to your access concerns.</p>
<p>4. Recommendation: The results of the NMA should be balanced with a comprehensive discussion of the uncertainties and limitations of this methodological approach within the Final Evidence Report.</p> <p>Rationale: ICER’s use of an NMA helps to support a simplified comparison of efficacy across DMTs, which is a key data need for PwMS and all stakeholders in the healthcare system. The NMA conducted in the current review represents significant improvements in methodological approach compared to that conducted by ICER in the 2017 review, and we commend ICER for their efforts to conduct a more robust clinical assessment. The current approach, assumptions, and sources used in ICER’s</p>	<p>We have added a discussion of the limitations of the NMA to our Uncertainties and Controversies section.</p>

	<p>NMA produced findings that are generally consistent with the existing body of evidence on comparative effectiveness. However, given the potential role of such evidence in informing access and treatment decisions, it is important that ICER contextualize the results with a robust discussion of both the strengths and limitations of applying NMA methods in the MS space.</p> <p>Due to the span of time over which the trials in the NMA were conducted and differences in study design, heterogeneity exists across DMT trials that may not be directly accounted for when utilizing NMA methods that do not adjust for cross-trial differences. Therefore, presentation of NMA results should be accompanied with a summary of effect modifiers and other differing cross-trial characteristics as well as their potential impact on results.</p> <p>Implications: Conclusions about comparative effectiveness derived via NMA should be balanced with a thorough discussion of limitations of the NMA methods and the underlying clinical evidence to ensure users of ICER’s report are fully apprised of how these limitations could create uncertainty or bias.</p>	
5.	<p>Recommendation: Revise assumptions in the CEA, as reasons and rates for discontinuation of first-line treatment and the subsequent second-line treatment basket do not reflect real-world clinical practice. Specifically, we propose that ICER:</p> <ul style="list-style-type: none"> <li>• Extend the treatment-specific discontinuation rates reported in Table 4.2 of the Draft Evidence Report beyond year two (i.e., throughout the model time horizon).</li> <li>• In line with standard HTA approaches, we recommend that ICER exclude second-line treatments in the base case CEA and focus the assessment on first-line treatment. For any scenarios including subsequent treatment, the second-line treatment basket should be varied based on first-line treatment to reflect that in real-world practice, patients would likely move to a treatment with a different MOA. We propose the following approach as one that is feasible within the existing model structure, though we acknowledge it is not a perfect representation of real-world practices that include additional treatment options and patterns of care: <ul style="list-style-type: none"> <li>○ Individuals who enter the model and initiate and discontinue an anti-CD20 (ocrelizumab, ofatumumab, ublituximab) as their first-line therapy would transition to a second-line treatment basket with cost and effectiveness equal to the average of natalizumab and dimethyl fumarate.</li> <li>○ Individuals who initiate and discontinue natalizumab as their first-line therapy would</li> </ul> </li> </ul>	<p>Evidence from the trials suggests discontinuation is highest after treatment initiation and then lowers. Our approach to discontinuation reflects that evidence. Further, we present numerous scenarios of subsequent treatments, including best supportive care as a second-line treatment. As can be observed in the report, so long as the second-line treatment is consistent between the intervention and comparator arms, the subsequent treatment has little influence over the findings and, rather, isolates the influence of the initially modelled treatment, which aligns with our objective. The best supportive care as second line, although presented as a scenario analysis, is not our base case because patients do not stop all DMT options if they discontinue one treatment.</p>

transition to a second-line treatment basket with cost and effectiveness equal to the average of ocrelizumab, ofatumumab, ublituximab, and dimethyl fumarate.

- Individuals who initiate and discontinue dimethyl fumarate as their first-line therapy would transition to a second-line treatment basket with cost and effectiveness equal to the average of ocrelizumab, ofatumumab, ublituximab, and natalizumab.

Rationale: The proposed assumptions for discontinuation fail to account for the many reasons patients discontinue treatment and are expected to result in significant overestimation of treatment duration.

- Discontinuation beyond two years: Current research does not support the assumption that discontinuation declines after two years, but instead shows a consistent trend in discontinuation for years after the initiation of the DMT
- Reasons for discontinuation beyond safety: Research has consistently shown that patients do not only discontinue MS DMTs due to AEs, but also due to perceived lack of efficacy, disease progression, non-compliance, insurance formulary changes, and the availability of new DMTs. Additionally, the use of DMTs declines with increases in EDSS scores, older age, and longer disease duration, particularly among patients with SPMS. Perhaps the most compelling reason to consider discontinuation reasons beyond the occurrence of serious AEs after two years is that current clinical practice guidelines recommend switching therapy due to new signs of disease activity from baseline.

With respect to second-line treatment, transitioning between DMTs with the same MOA after treatment failure is not reflective of clinical practice nor is it consistent with American Academy of Neurology practice guidelines, which state, “when a patient shows breakthrough disease activity (continued relapses, MRI activity), trying a medication with a different mechanism or efficacy profile may be beneficial.” Among the interventions in the assessment, ocrelizumab, ofatumumab, and ublituximab have the same MOA, and, therefore, switching between these treatments after breakthrough disease activity is unlikely.

Finally, sequential treatment assessment is not representative of best practice approaches taken by global HTA bodies. For example, in their reviews of ocrelizumab and ofatumumab, both NICE and CADTH assume that after

	<p>discontinuation of the first-line treatment, patients transition to best supportive care to solely assess the value of first-line treatment in modeling exercises.</p> <p>Implications: Treatment assumptions in the CEA are not reflective of clinical practice, guideline recommendations, or methodological best practices, and bias the assessment towards overestimated cost-effectiveness ratios for all interventions of interest.</p>	
6.	<p>Recommendation: Remove Scenario Analysis 7 in entirety, or revise Scenario Analysis 7 to estimate the impact of incorporating treatment-specific CDI for all interventions of interest.</p> <p>Rationale: The emergence of high-efficacy DMTs has raised awareness of the importance of CDI as a long-term outcome; CDI is increasingly used as a measure in trials and may be an important consideration in treatment selection. Thus, while CDI has typically been limited to an exploratory endpoint in more recent trials as a better scientific understanding of CDI is still needed, investigating the potential ability of a treatment to restore function as a scenario analysis within the CEA may present a more holistic assessment of the true impact of these treatments for PwMS.</p> <p>While ICER has made efforts to integrate exploratory trial data on CDI for ublituximab, it has failed to take a consistent approach and do the same for the other interventions of interest, which all have reported CDI data from pivotal trials. To support an objective and balanced assessment, ICER should either remove Scenario Analysis 7 or, alternatively, leverage treatment-specific CDI data from the respective pivotal trials for all interventions, such that the corresponding value assessment of ublituximab can be better evaluated relative to other treatments.</p> <p>Implications: Failure to take a consistent approach in modeling treatment impacts for all interventions may result in a biased assessment and limits the ability of readers to objectively consider the relative value of the treatments included in the CEA.</p>	<p>We have removed scenario analysis 7 from the report given the limited and inconsistent data available on CDI for the modeled interventions. We explored CDI as some treatments do have evidence, but data overall was insufficient to include in the model findings.</p>
7.	<p>Update the model base-case to exclude direct healthcare costs unrelated to MS to better align the base-case assumptions and costing approach with the standard ICER and HTA methods.</p>	<p>In alignment with the ICER Reference Case and with recommendations from the Second Panel, we include future related and unrelated health care costs (Sanders 2016 et al).</p>
8.	<p>The Markov traces for all interventions appear to account for treatment costs and discontinuation without accounting for the impact of treatments or allowing patients to transition to other health states and death in cycle 0. Clinical trials have demonstrated efficacy benefits for MS therapies within the first year of starting treatment. Update cycle 0 calculations to include the treatment benefit. Include the half-cycle correction to account for the fact that</p>	<p>We have updated our assumption that transitions occur at the end of the cycle to transitions occur at the beginning of the cycle, thereby allowing for a treatment benefit in the first cycle given the information provided that demonstrated efficacy can occur in the first few weeks/months. This change also addresses aspects of the half-cycle correction, as we are now optimistically assuming transitions happen at the very beginning of the cycle (rather than the midpoint or the end).</p>

	transitions can occur at any point during each one-year cycle.	
<b>Novartis</b>		
1.	<ul style="list-style-type: none"> <li>Novartis recommends that ICER consider a more comprehensive and high-quality evidence base to inform network meta-analyses.</li> </ul> <p>A key advantage of an NMA is it uses both direct and indirect evidence to generate treatment effect estimates. These estimates are more robust because they are informed by multiple sources of evidence (Dias and Caldwell, 2019). In the MS space, there are many RCTs for interferon therapies and glatiramer acetate that are important sources of indirect evidence for NMAs. A review of full-text peer-reviewed publications by Novartis identified 41 relevant articles for inclusion compared to 22 identified by ICER. (Novartis data on file; manuscript in progress, and draft can be shared with ICER upon request). A more comprehensive review of evidence feeding into the NMA will allow for additional connections within ICER’s evidence networks, producing more robust estimates.</p> <p>Although it is important to use a comprehensive evidence base to inform an NMA, input data should only be obtained from full-text pivotal RCT publications that have undergone peer review to ensure the highest quality of evidence is used. As highlighted in the Cochrane Handbook for Systematic Reviews of Interventions, the information available in conference abstracts can vary substantially in terms of its accuracy and reliability (Li et al., 2022). Consequently, data from conference abstracts may not be appropriate for an NMA (e.g., 6-month CDP data for the PRISMS trial (PRISMS 1998)) or may warrant inclusion only as a sensitivity analysis.</p> <p>Therefore, Novartis recommends that ICER consider: 1) a more comprehensive evidence base that includes data from pivotal RCTs for interferon therapies and glatiramer acetate, and 2) a high-quality evidence base consisting of peer-reviewed RCT data only (i.e., include data from full-text pivotal RCT publications and exclude data from conference abstracts) to estimate comparative efficacy via NMAs and inform the economic model.</p>	<p>Our review was not focused on all DMTs but on oral and monoclonal antibody treatments for relapsing forms of MS. As such, we limited our studies to the direct and indirect evidence relevant to the interventions in our scope.</p> <p>As noted in our Value Assessment Framework, ICER includes evidence from the “grey literature” per <a href="#">our criteria</a>. We supplement our reviews of studies from peer-reviewed publications with data from conference proceedings, regulatory documents, materials from other HTA groups, information submitted by manufacturers, and input gleaned from patients. Consideration of multiple sources of evidence helps us evaluate whether there is a biased representation of study results in the published literature and provides an all-encompassing understanding of the net health benefit of a treatment.</p>
2.	<ul style="list-style-type: none"> <li>Novartis recommends that ICER use reanalyzed CDP data from ASCELPIOS I/II to reduce bias in modelled indirect comparative efficacy estimates.</li> </ul> <p>The definition of CDP has several components, including increase in EDSS score required to be considered progression, definition of baseline EDSS score, confirmatory time window during which initial progression had to be sustained to be considered confirmed, and method of confirming progression. These components collectively define CDP in clinical trials. As noted in Section D2 of</p>	<p>As noted in our NMA Limitations section, the slight variation in the definition of the CDP across trials is a potential source of bias. Therefore, the attempt to align the CDP definition in the ASCELPIOS I/II to that of the ocrelizumab and ublituximab trials, although post-hoc, is informative. And as such, we have included this reanalyzed CDP data (submitted as academic-in-confidence) as a scenario analysis. However, we did not use this in our base-case analysis for two important reasons: 1) Given the post-hoc nature of this data and other potential differences that couldn’t be addressed using this analysis, it would be important for us to interpret this data with caution, and 2) We believe the company had access to this data when</p>



<p>Appendix D (NMA Limitations) of the draft ICER report, there were variations in the definition of CDP across trials included in the NMAs.</p> <p>Increasing the alignment of outcome definitions across trials for therapies included in an NMA is an important means of reducing bias by reducing the impact of outcome definitions (such as CDP) on efficacy estimates. To address this source of cross-trial heterogeneity, Novartis conducted an NMA including outcomes such as 3-month and 6-month CDP using reanalyzed CDP data for the ofatumumab ASCLEPIOS I/II trials. Specifically, the CDP data for ASCLEPIOS I/II were reanalyzed (EDSS-aligned CDP) to align with the EDSS score increases used to define CDP in multiple comparator trials including the ocrelizumab OPERA I/II trials and the ublituximab ULTIMATE I/II trials. The reanalyzed ASCLEPIOS I/II EDSS-aligned CDP data have not yet been published but can be made available to ICER upon request. NMAs conducted by Novartis using the ‘EDSS-aligned CDP’ data for ASCLEPIOS I/II were included in the submission for ofatumumab to the National Institute for Health and Care Excellence or NICE (referred to as CDW-6 aligned CDP by NICE), which they implemented in their technology appraisal as base case analysis (NICE, 2021).</p> <p>Relative to the per-protocol CDP, the use of ‘EDSS-aligned CDP’ data for ASCLEPIOS I/II permits greater alignment with both OPERA I/II (Hauser 2017) and ULTIMATE I/II (Steinman 2022) in terms of the magnitude of increase in EDSS score required to be considered progression. As a result, an NMA conducted using the ‘EDSS-aligned CDP’ data for ASCLEPIOS I/II would be expected to be less impacted by bias due to heterogeneous outcomes. Although this does not eliminate the heterogeneity observed in CDP outcome definition, it certainly reduces it to make indirect comparative estimates more meaningful.</p> <p>Therefore, in order to adjust for underlying differences in how clinical trials define CDP, Novartis recommends using the EDSS-aligned definition of CDP as base case to allow for more consistent and less biased estimation of disease progression across the included trials.</p>	<p>we started our review in April 2022. The manufacturer had prior opportunities, including a direct data request, to submit this data to us, however, this is the first time we are learning of it. Therefore, using this data in our base case without allowing other stakeholders to provide their comments would be unfair, particularly given the post-hoc nature of the data.</p>
<p>3.</p> <ul style="list-style-type: none"> <li>Novartis recommends that ICER acknowledge more prominently the methodological limitations of NMA in addressing cross-trial heterogeneity in patient population characteristics, and its implications for comparing efficacy outcomes across trials.</li> </ul> <p>There is considerable heterogeneity in baseline characteristics of patient populations included in trials for MS drugs. For example, patient baseline characteristics differed between the ASCLEPIOS I/II (Hauser 2020, Gärtner 2022) and OPERA I/II (Hauser 2017) populations, specifically with regards to normalized brain volume, prior DMT</p>	<p>We have added a discussion of the limitations of the NMA to our Uncertainties and Controversies section.</p>

	<p>experience, time since MS diagnosis, time since first MS symptoms, volume of T2 lesions, and age. Overall, the comparison of baseline characteristics suggests the ASCLEPIOS I/II population was a more experienced MS population compared with the OPERA I/II population.</p> <p>The impact of cross-trial heterogeneity on efficacy outcomes is made clear in a recent simulated treatment comparison (STC) by Samjoo et al. (2022) that compared ofatumumab and ocrelizumab. Leveraging patient-level data for ofatumumab, the STC analysis not only accounted for CDP outcome variability but also cross-trial heterogeneity among patient populations. Specifically, to limit the bias introduced by outcome definition variability, the CDP data for the ofatumumab ASCLEPIOS I/II trials were reanalyzed to align fully with the reported CDP definition used in the ocrelizumab OPERA I/II trials. While the ICER NMA shows lower hazard ratios for ocrelizumab than for ofatumumab for both CDP outcomes, the STC analysis shows that after adjusting for cross-trial heterogeneity, the point estimates for various outcomes shift in favor of ofatumumab. These findings exemplify the limitations of NMA in addressing potential bias introduced by cross-trial heterogeneity.</p> <p>Therefore, we request that ICER address any source of bias that can be accounted for within a NMA framework (such as alignment of CDP definition across trials) and prominently acknowledge potential impact on findings of biases that cannot be addressed within a NMA framework (such as cross-trial heterogeneity in patient characteristics).</p>	
<p>4.</p>	<ul style="list-style-type: none"> <li>Novartis recommends that ICER use drug cost estimates that more accurately account for real-world mark-ups on infusible DMTs.</li> </ul> <p>Evidence gathered from 3 separate studies conducted using different data sources consistently demonstrates that real-world costs of treating MS patients with infusible DMTs is significantly higher than their WAC price. In a retrospective observational cohort study of MS patients initiating IV DMTs conducted using the HealthCore Integrated Research Database, Alvarez et al (2021) found that real-world IV treatment and medical costs for commercially insured patients in the first year of treatment were ~20%-60% higher than the drug costs based on WAC (20% higher for natalizumab; 38% higher for alemtuzumab; and 60% higher for ocrelizumab). Similar trends were reported by Dieguez et al (2019) using IBM MarketScan Commercial Claims Data and by Nicholas et al (2020) using the Optum Research database. Moreover, studies have found that subcutaneous products across therapeutic areas offer numerous economic advantages when compared with infusible products due to the higher provider-administration costs, premedication requirements, and drug wastage costs associated with infusible products (Anderson 2019, Epstein 2021).</p>	<p>Importantly, we do model additional provider-administered mark-up costs and administration costs for infused interventions. We continue to look for a better source for mark-up costs for commercially insured patients, but have concerns with the “small sample size, limited population generalizability,” and the focus on treatment initiation rather than average treatment costs within the citations provided. We added a paragraph to the Uncertainties section of Section 4 that emphasizes the different costs between infused and subcutaneous treatments, but we have kept the 6% mark-up for provider-administered treatments in the model. Also, we model a higher first year cost than subsequent year costs if the evidence suggests.</p> <p>Also, per the manufacturer of ofatumumab and after reviewing the label for ofatumumab, we have updated the maintenance year dose for ofatumumab to be once monthly, rather than once every four weeks.</p>

	<p>Novartis believes that ICER’s use of average net price for infusible monoclonal antibody DMTs included in the review likely under-estimates the true cost of infusible DMTs and biases the incremental cost effectiveness ratio in their favor. Therefore, we suggest that ICER apply a percentage mark-up to the cost of infusible DMTs that is in line with multiple real-world studies.</p>	
<p>5.</p>	<ul style="list-style-type: none"> <li>Novartis recommends that ICER incorporate indirect treatment costs into the base-case analysis.</li> </ul> <p>MS is a leading cause of nontraumatic disability in young to moderately aged individuals, and nearly 30% of individuals with MS in the US are reliant on public disability insurance (eg, Social Security Disability Insurance) (Iezzoni 2007). Additionally, the indirect costs of lost productivity are substantial, and employees with MS have been found to have disability and absenteeism-related costs that are four times that of employees without MS (Ivanova 2009). In a recent study of the total economic burden of MS in the US, researchers estimated the total indirect costs associated with MS in 2019 were \$21.0 billion (or 25% of the total economic burden of the disease), with approximately \$16.8 billion attributable to patients with MS and \$4.2 billion attributable to unpaid caregivers (Bebo 2022). The authors also found that premature death accounted for the largest share of indirect costs (\$8.0 billion; 38%), followed by presenteeism (\$5.9 billion; 28%) and absenteeism (\$5.6 billion; 26%) and that the costs of absenteeism and presenteeism for the caregivers were about half of those for patients with MS (Bebo 2022). Therefore, we recommend that ICER consider incorporating indirect treatment costs into the base case analysis.</p> <p>Furthermore, we suggest that ICER include caregiver time cost and disutility into the cost-effectiveness model, as has previously been done by NICE (NICE 2007, NICE 2012, NICE 2014, NICE 2021). A recent study by Koeditz et al. showed the impact of including indirect costs in the analysis, noting that they contribute more than 30% of the total costs in the modeled population, which would significantly affect a cost-effectiveness ratio (Koeditz 2022).</p> <p>In concluding our response to the draft evidence report, we appreciate the opportunity to provide comments for this assessment, and respectfully request consideration be given to the points we have made to ensure a scientifically sound and robust assessment.</p>	<p>We use the source mentioned (Bebo 2022) in our analysis that takes the modified societal perspective. In this perspective, we include costs not only for the primary caregiver but also for the secondary caregiver. We include costs to the primary and secondary caregiver related to early retirement, absenteeism, presenteeism, and social productivity loss in volunteer work. We did not identify a suitable source that suggests caregiver quality of life significantly varies by EDSS score. In alignment with ICER’s Reference Case, the modified societal perspective was not presented as a co-base-case analysis because the impact of the treatments on patient and caregiver productivity was not substantial. Further, the cost-effective threshold is based on health impacts only and doesn’t include broader societal opportunity costs.</p>
<b>Sanofi</b>		
<p>1.</p>	<p>Sanofi encourages ICER to include novel endpoints, such as CDI as part of the network meta-analysis.</p> <p>Despite acknowledging the importance of a broader set of endpoints in the revised scoping document, ICER’s indirect treatment comparisons between the interventions of</p>	<p>We explored the inclusion of CDI as an outcome. However, it was available for a small fraction of the RCTs in our NMA and varied in length for which the improvement was sustained (three or six months). Therefore, we concluded that there was insufficient evidence across our trials to allow for this comparison.</p>

	<p>interest is limited to CDP and reductions in ARR. Multiple clinical trials have reported CDI results, and we respectfully request that ICER discuss whether it conducted a feasibility analysis of conducting the NMA using CDI and clarify to what extent it would be possible to conduct any comparisons between the interventions of interest.</p>	
2.	<p>Sanofi encourages ICER to consider real-world evidence for teriflunomide when evaluating the net health benefit. ICER’s current assessment of the net health benefit of ublituximab vs. teriflunomide appears to be based exclusively on ublituximab’s phase III trials and the observed differences in the reduction of ARR. Given the absence of statistically significant differences in disability progression, which ICER acknowledges throughout its report as the most important endpoint for patients and providers, ICER’s conclusion of an incremental benefit (B) appears to be driven by ARR and discounts the importance of demonstrating statistically significant benefits in disability outcomes as well as the need to generate long-term safety and efficacy data.</p> <p>Teriflunomide was approved in the United States for the treatment of relapsing forms of MS in September 2012. Teriflunomide’s long-term safety and efficacy are very well characterized with 114,400 patients treated globally. During the review process, Sanofi also provided relevant publications, substantiating teriflunomide’s real world effectiveness. Thus, we ask ICER to consider the totality of the evidence provided for teriflunomide, acknowledge the importance of real-world evidence, and assign a net health benefit rating in accordance with the body of evidence supporting the merits of each intervention.</p>	<p>We noted that teriflunomide has demonstrated safety in long-term studies (page 18). While we appreciate that there is uncertainty about the long-term safety of ublituximab and have acknowledged this in our report, our evidence rating reflects that in the head-to-head trial data from ULTIMATE I and II, ublituximab demonstrated statistically significant improvement in ARR and the data on CDP numerically favored ublituximab as well. Additionally, numerous secondary outcomes also favored ublituximab (e.g., CDI, improvement in MSFC, number of MRI lesions). Our evidence rating reflects these findings.</p>
3.	<p>Sanofi recommends more transparency on ICER’s choice of NMA trial network to derive the RR of disease progression used in the cost-effectiveness model. ICER cites the results of the NMA as the source for the RR CDP estimates (Table E7, p. E12) used in the cost-effectiveness evaluation, but the number of interventions included in the NMA is much more extensive than the interventions included in the cost-effectiveness model. We respectfully request ICER to disclose whether a separate NMA, limited to the interventions included in the economic model, was conducted to inform the RR estimates or whether it relied on RR estimates from the original NMA with a broader set of comparators. We feel that the former approach would be the more appropriate choice given the interventions included in ICER’s cost-effectiveness model.</p>	<p>Please see Supplement D2 for a detailed description of the NMA methods and trials included. To clarify, we conducted a single NMA model to estimate the hazard ratios for time-to-disability progression for both the clinical and cost-effectiveness sections. We believe this is the most appropriate approach because it keeps our message consistent in both sections of the report.</p>
4.	<p>Sanofi believes that the report can benefit from greater clarity on the treatment benefit assumptions once patients have transitioned to SPMS in the cost-effectiveness model. The current model assumes (Table E3, p. E9) that patients will continue treatment with their MS medication once they have transitioned to SPMS. ICER justified this assumption based on the input from clinicians. However, it is unclear why the model also assumes that the treatment benefits</p>	<p>The treatment benefit in SPMS is for both disability progression and relapse. We have made this assumption more explicit in the report. It may be an optimistic assumption for the modeled interventions as we heard that patients would continue treatment even with SPMS, but efficacy is more uncertain than with RRMS. We have programmed the flexibility of the model to allow for different efficacy assumptions in SPMS. The <a href="#">Interactive Modeler</a> can be</p>

	<p>would also persist during the SPMS phase of the condition. It should be noted that natalizumab, ocrelizumab, and ofatumumab’s indications only include “active” SPMS, and thus any assumed benefits should be limited to reductions in the occurrence of relapses and not on slowing disability progression. While ublituximab has yet to be approved in the US, given that the analysis is focused on “relapsing forms of MS,” a similar assumption of no treatment effect on disability progression once patients transition to SPMS is warranted. Whether ICER already assumed that treatment benefits are limited to relapse reductions during the SPMS phase is unclear and we request that this is discussed more explicitly.</p>	<p>used to examine the influence of these alternative assumptions on the economic findings.</p>
<p>5.</p>	<p>Page 7: The baseline distribution of patients in Table E2 of the report only refers to RRMS.</p> <p>Comment: The focus of the analysis is on “relapsing forms of MS”, which should include CIS, RRMS, and SPMS. The baseline distributions by EDSS score in Table TBD would suggest that only RRMS patients are included in the analysis.</p> <p>Recommendation: Please consider removing “RRMS” from the table and only describe the baseline distribution based on EDSS scores. Alternatively, if the analysis is solely focused on RRMS, please clarify throughout.</p>	<p>All patients start in RRMS but can progress to SPMS over the model time horizon. This was because the studies that provided granular data on baseline EDSS state were 100% RRMS at baseline.</p>
<p>6.</p>	<p>Page E20: The economic model uses the same cost of relapse data from the 2017 ICER assessment of MS treatments despite the availability of more recent sources.</p> <p>Comment: By relying on dated sources for the cost of relapses, ICER could be underestimating the true cost of a MS relapse, and thus undervaluing the potential cost-offsets associated with reductions in ARR.</p> <p>Recommendation: Please update cost of relapse estimates based on more recent sources, such as Parisé et al or Nicolas et al</p>	<p>As noted in our report, we use the Parisé source to update the cost of relapse data from the 2017 ICER assessment. From this source, we estimate a cost differential in relapse based on severity.</p>
<p>7.</p>	<p>Page E19: The economic model uses the cost generic DMF rather than a blended price of branded and generic DMF as it occurs in practice.</p> <p>Comment: By utilizing the cost of generic DMF and ignoring the use of branded TECFIDERA, ICER is implicitly assuming that 100% of the utilization of DMF in practice is generic, when in fact this is not the case.</p> <p>Recommendation: Please adjust the cost of DMF to reflect its actual use in practice by using a blend of branded TECFIDERA and generic DMF pricing. There is precedent for considering the price erosion of a generic in light of the continued utilization of some branded product<sup>20</sup>, which could help inform the cost of DMF assumption or a simple blended price of generic weighted by actual utilization could be considered.</p>	<p>Our approach to estimating the cost of dimethyl fumarate is in alignment with our reference case.</p>

**TG Therapeutics**

<p>1.</p>	<p>Limitation 1: The internal validity of the network meta-analysis (NMA) CDP results has been impacted due to the introduction of older and single-blind trials.</p> <p>ICER aptly detailed limitations of trial data included in the NMA in the supplemental section of the comparative efficacy assessment (ICER 2022 DER, page D13). The CDP NMA could only include ocrelizumab and ozanimod by introducing older and single-blind trials, respectively: “Due to data limitations, we had to introduce some older trials in our CDP NMA (PRISMS and BRAVO) to allow us to include ocrelizumab and ozanimod, which were only compared to interferon 44 mg and interferon 30 mg, respectively” (ICER 2022 DER, page D13). In order to connect ocrelizumab to the CDP NMA network, PRISMS, an interferon study from nearly 30 years ago had to be utilized. Including this trial in the network could lead to bias given that the treatment landscape for MS has dramatically advanced since the PRISMS trial was conducted. Similarly, BRAVO, a single-blind study, was utilized to connect ozanimod to the network for the CDP, which raised some concern in ICER’s risk of bias assessment within the randomization process, missing outcomes, and overall bias.</p> <p>The fact that the CDP results are contingent on PRISMS and BRAVO raises concerns about ICER’s conclusions. Although we recognize ICER’s transparency on this limitation, it is important to note how the use of these two trials impacts the applicability of the results. These limitations should be emphasized within the body of the report when the results of the CDP NMA are reported and reiterated when the CDP results are utilized for additional supplemental conclusions of relative CE of ocrelizumab and ozanimod.</p>	<p>We disagree that the internal validity of the NMA CDP result was impacted due to the introduction of PRISMS and BRAVO. Although we noted this as a potential source of heterogeneity, we conducted a sensitivity analysis where we excluded both trials from our analysis. The exclusion of these trials did not change the result for any intervention for CDP-6 and CDP-3 (see Supplement D2). Therefore, our decision to use these trials in the base-case NMA did not introduce any major bias into our estimates for ublituximab and the other interventions.</p>
<p>2.</p>	<p>Limitation 2: Different definitions of CDP and varying proportion of patients who received prior DMT impact the applicability of results.</p> <p>ICER states that “there were slight variations in the definition of CDP across trials and in the proportion of patients who had received prior DMT” (ICER 2022 DER, page D13). Table A1 in the appendix shows how CDP definitions and cut-offs varied between trials. Given the varying CDP definitions across trials and the significant impact of CDP on the structure and outcomes of the model, it is important that ICER acknowledge the uncertainties of the computations regarding CDP in Sections 4.3 (Results) and 4.4 (Summary and Comment) of the DER. Such uncertainty compromises the interpretation of ICER’s CE findings.</p>	<p>This limitation, which was described in the NMA section, is acknowledged and has been further discussed in the Uncertainties and Controversies section.</p>
<p>3.</p>	<p>Limitation 3: Disability progression data from the respective pivotal trials raise concerns about the key drivers of the CE analysis.</p>	<p>This limitation was acknowledged in the Clinical and Cost Effectiveness sections of the report.</p>



	<p>As evidenced by the one-way sensitivity analysis, the primary driver of ICER’s CE analysis is the hazard ratio on EDSS progression, which was derived from ICER’s NMA of CDP at 6 months (CDP-6). In its NMA, ICER acknowledges that the credible intervals for the point estimates of CDP-3 and CDP-6 “were wide and are reflective of the uncertainty measuring disability progression” (ICER 2022 DER, page 15). Measuring disability progression across a duration of three or six months in a two-year MS trial raises additional concerns about the CE results. Moreover, “the time to CDP-6 network was particularly underpowered” because the majority of NMA trials were not powered to detect a significant difference for this endpoint (ICER 2022 DER, page 15). Since CDP-6 was the key clinical effectiveness measure in the CE analysis, the use of this endpoint further indicates uncertainties about the NMA results and any conclusions that are derived from the base case and sensitivity analyses.</p>	
4.	<p>Limitation 4: Due to varying treatment practices, it is unclear what proportion of patients remain on DMTs at advanced stages of disease in the real world.</p> <p>In the 2017 ICER assessment, the CE model assumed that treatment was stopped once patients progressed beyond EDSS 7. Similarly, the economic analyses in CADTH’s RMS assessment and NICE’s 2021 assessment of ofatumumab assume that treatment stops at EDSS 7. However, the current ICER assessment assumes that treatment continues until death, which has important implications for the findings from the model. In Section E5 of the DER, scenario analyses 3 evaluates the impact of stopping treatment after a patient has reached an EDSS higher than 7 (ICER DER, page E29). A decrease of \$72,000 per QALY gained was observed for ofatumumab, followed by decreases of \$51,000 per QALY gained for ublituximab and natalizumab and \$10,000 per QALY gained for ocrelizumab. Thus, the CE ratios of all monoclonal antibodies decrease compared to the base case.</p> <p>It is important to note that ICER acknowledged that “there is no clinical consensus as to when treatment should stop” (ICER DER, page 26). Yet ICER’s assumption for continuing treatment over the patient lifetime in its model was based on what ICER “heard from clinical experts” (ICER DER, page 26); the specificity of these discussions (e.g., which clinicians, how many clinicians, transcripts) is not transparent. Nevertheless, treatment effectiveness with DMTs is highest during the early stages of EDSS. This is most attributed to the fact that at advanced stages of MS, the neurodegenerative component in the pathophysiology of MS is not or no longer responsive to immunotherapy and the primary site of action is not directly in the central nervous system. Since there is no clinical consensus on the use of treatment beyond EDSS 7, a more conservative base case assumption should be to discontinue DMTs at later</p>	<p>We include the discontinuation of treatment for EDSS scores greater than 7 in a scenario analysis. Please refer to the comment within this document from the MS Coalition on how clinical advisors disagreed with the assumption that EDSS 7 is an appropriate cutoff. They suggested that a later discontinuation assumption would be a more reasonable assumption. We have kept the scenario of discontinuation at an EDSS of greater than 7, but acknowledge that clinical experts suggest discontinuation that early may be inappropriate.</p>

	EDSS stages as opposed to reserving this assumption for a scenario analysis.	
5.	<p>A balanced narrative of all monoclonal antibodies should be provided.</p> <p>ICER indicated, in several publicly released documents preceding the DER, that the assessment would focus on comparing agents within the monoclonal antibody class to one another as well as against leading oral therapies. Despite setting the expectation of a balanced assessment of DMTs prior to the DER, ICER focused the reporting of its comparative clinical effectiveness analysis in the DER disproportionately on ublituximab. We would have expected, therefore, a more balanced assessment across DMTs within the discussion, particularly since there have been other agents approved by the FDA (e.g., ocrelizumab, ofatumumab) since ICER’s 2017 MS class review. In particular, the executive summary should clearly state ICER’s conclusions that the overall class of monoclonal antibodies are highly effective but none of those agents meets ICER’s threshold for cost effectiveness. To this point, ICER’s concluding text in the executive summary is not consistent with the presentation in Section 4.4. (Summary and Comment), which reads: “At their estimated net prices including the placeholder price assumed for ublituximab, each intervention is expected to exceed standard cost-effectiveness levels in the US health care system.” (ICER 2022 DER, page 33) This text, presented in Section 4.4, should also be used in the executive summary.</p> <p>Recommendation: ICER should consider reframing the executive summary and comparative clinical effectiveness sections to include an equal and balanced comparison of each monoclonal antibody (i.e., ocrelizumab, ofatumumab, natalizumab) to alternative DMTs.</p>	<p>We have considered these recommendations. One of our goals is to compare DMTs to each other, particularly at the class level. However, in line with other ICER reviews of newly-emerging therapies, we also focused on comparing ublituximab to other DMTs as ublituximab is the newest DMT currently under FDA review. Additionally, the structure of our report is meant to inform decisions about how ublituximab will be used for MS treatment. In our report, we have attempted to clarify when we are comparing agents within/across classes, and why we have focused on ublituximab for some of our comparisons.</p>
6.	<p>Only interventions and comparators that have, or are currently seeking, FDA-approved indications in MS should be included.</p> <p>ICER’s DER includes the assessment of rituximab in its comparative clinical effectiveness evaluation. While we recognize that rituximab and recent biosimilar formulations are used in off-label treatment for MS, rituximab is not currently indicated for the treatment of MS nor is there an FDA-approved dose for rituximab nor its biosimilar formulations. Moreover, the quality of clinical data is expected to be consistent across approved and investigational therapies for MS; discrepancies may exist in clinical trial design for off-label therapies including rituximab, thereby preventing appropriate comparisons. For instance, ICER included the RIFUND-MS trial in the present analysis, which was new to this evaluation compared to the 2017 assessment, to evaluate rituximab’s benefit on ARR. However, there are dissimilarities with the RIFUND-MS trial</p>	<p>Our review of the literature suggests that rituximab is used for the treatment of MS both in the United States and abroad, and clinical experts and patient groups confirmed that rituximab is an important part of the treatment arsenal, even if it does not have a label for MS treatment. Given that new data has emerged regarding the efficacy of rituximab, we feel it is important to include it in our report to ensure that stakeholders are able to assess the value of rituximab treatment alongside other commonly used DMTs.</p>

	<p>population compared to the populations evaluated in other DMT trials, suggesting that patients in the RIFUND-MS trial had less severe disease. Mean baseline EDSS scores in the RIFUND-MS trial (mean [SD] for rituximab: 1.6 [1.2]) were substantially (numerically) lower than mean scores from the pivotal trials of the other monoclonal antibodies under study (ULTIMATE I and II for ublituximab {2.96 [1.2], 2.8 [1.3]}, OPERA I and II for ocrelizumab {2.9 [1.2], 2.8 [1.3]}, ASCLEPIOS I and II for ofatumumab {2.97 [1.4], 2.9 [1.3]}, despite potential overlap based on standard deviations. These are substantial differences based on the definitions of EDSS 1.5 (no disability, minimal signs in more than 1 functional system [FS] score) compared to EDSS 3.0 (moderate disability in 1 FS or mild disability in 3 or 4 FS). Additionally, the proportion of trial participants on prior DMT use in the pivotal trials for the other monoclonal antibodies (range: 26- 60%) was substantially (numerically) higher than the proportion in the RIFUND-MS trial (about 0%), suggesting higher prior DMT failure and likely greater disease severity in the other monoclonal antibody trials.</p> <p>Recommendation: ICER should remove rituximab from the comparative clinical effectiveness evaluation for the reasons stated above.</p>	
7.	<p>Adjustments regarding biosimilars should be made in the economic modeling analyses</p> <p>A scenario analysis in ICER’s CE analysis compared each intervention to a hypothetical monoclonal antibody biosimilar by making assumptions regarding the biosimilar’s treatment effectiveness. This is concerning for two reasons. First, based on ICER’s sensitivity analysis, the model is highly sensitive to the relative treatment effectiveness of the primary intervention (i.e., the hazard ratio of EDSS progression). Second, rituximab and its biosimilar formulations do not have clinical data regarding CDP and EDSS, as evidenced by ICER’s inability to include rituximab in its CDP NMA. Therefore, without robust clinical evidence, it is inappropriate to make strong assumptions on the biosimilar’s treatment effectiveness given how sensitive the model is to this parameter. Additionally, in the budget impact assessment, ICER overstated the market share of the rituximab originator and its biosimilars (45%), as current real-world data suggests a declining market share that currently stands at ~5% as of Q2 2022 (data on file as of 11/8/22).</p> <p>Recommendation: ICER should remove the hypothetical monoclonal antibody biosimilar scenario analysis in the CE analysis and budget impact assessment for the reasons stated above.</p>	<p>The hypothetical biosimilar comparator is not our base case, doesn’t factor into our health-benefit price benchmarks, and is only presented as a scenario analysis. There are MS monoclonal antibody biosimilars (not rituximab) in the pipeline, so there is policy relevance to this scenario. A placeholder price for this potential biosimilar comparator was based on the price of biosimilar rituximab, which is another monoclonal antibody.</p> <p>The 45% market share we assumed for rituximab in the budget impact analysis was based on clinical expert opinion suggesting it would be similar to ocrelizumab. We acknowledge the limitation of this in our report. Given that the market share you provide is confidential, we are unable to assess the evidence appropriately. We also model a scenario in the budget impact analysis assuming 0% rituximab.</p>

#	Comment	Response/Integration
<b>Patient/Patient Groups</b>		
<b>Multiple Sclerosis Coalition</b>		
1.	<p>We note several factors that are important for readers to note when interpreting and considering how to apply results presented in the draft evidence report:</p> <ul style="list-style-type: none"> <li>• As a highly heterogeneous disease with significant variation in disease course and severity, multiple factors and individual characteristics can impact treatment effectiveness. Different treatments will work for different individuals.</li> <li>• Several generic DMTs are expected to become available in the near future</li> <li>• The opaque pricing system, including various discounts and rebates in the current market leave a great deal of uncertainty in the results</li> <li>• There is a lack of diversity across clinical trial populations and the findings may not be generalizable to all PwMS</li> </ul> <p>We recommend ICER consider including these considerations throughout the report.</p>	<p>Thank you for your thoughtful comments. We have included language in the report to reflect heterogeneity in disease course, the future emergence of generic DMTs, and the lack of diversity across clinical trials. We agree that determining accurate pricing is challenging in our current health care system and we have acknowledged this as well in the Patient Perspectives section.</p>
2.	<p>We are concerned that the language and visuals reporting results of the NMA do not adequately reflect study heterogeneity and uncertainty. Table 3.1 describes significant differences across the clinical trials included in the NMA. We believe it is important that the forest plots depicted on page 12 are interpreted in the context of heterogeneity across studies. We suggest that footers are inserted below each of the forest plots referring readers to Table 3.1 to understand heterogeneity across studies.</p> <p>Similarly, we believe that conclusions may be overstated on page 13 regarding "Relapse Rate" given the large and overlapping confidence intervals. We recommend including confidence intervals in the conclusion about ponesimod and including a statement about uncertainty of the results.</p>	<p>The use of a forest plot to depict the results, rather than a table, was actually intended to illustrate how the CIs overlap for CDP outcomes, reflecting a lack of statistical differences between the interventions on this outcome. Although there was some heterogeneity in the trials informing our NMA, we believe they were sufficiently similar in terms of trial design, eligibility criteria, and important patient characteristics to be included in the NMAs. We have expanded our discussion on the NMA limitations in the Controversies and Uncertainties section and provided an additional discussion in Supplement D2. In addition, we have added a footnote to the forest plot to refer the reader to the trials that informed the analyses. Furthermore, to maintain consistency with the rest of the agents in the Relapse Rate subsection, we have added 95% CI values to ponesimod and teriflunomide.</p>
3.	<p>We note an important error on Page 1, paragraph 3: the report states that 20% of those with RRMS progress to SPMS and references a study by Binzer and colleagues. However, that paper looked at the association of depression and disability progression. A study by Barzegar and colleagues estimated incidence rate of progressive MS was 17.8% during the entire study period. The 50% risk for convert from RRMS to SPMS was 20 years.</p>	<p>This statement has been corrected to reflect the higher risk of conversion from RRMS to SPMS.</p>
4.	<p>Variations in clinical practice patterns: To ensure representativeness of clinical perspectives on ICER's voting panel, we recommend that ICER includes clinicians working in various settings of care, including non-academic, community settings.</p>	<p>The New England CEPAC is a diverse committee comprised of clinicians practicing in multiple settings of care, patient advocates, health economists, and health services researchers. This council will be deliberating on ICER's report at the January 20, 2023 Public Meeting.</p>
5.	<p>Potential harms: Clinical advisors to the MS Coalition recommended that data on potential harms that impact prescribing patterns should be based on extension study data, since they increase over time. Clinicians note that</p>	<p>The Harms section of the report notes the risk of infection and low immunoglobulins associated with monoclonal antibody DMTs. This section was revised to also include the impact of hypogammaglobulinemia on administration of live vaccines.</p>

	major harms associated with MABs, especially B-cell therapies, are infection risks and low immunoglobulins, which increase over time and prompted IgG and IgM monitoring recommendations for ocrelizumab. Similarly, PML risk with natalizumab and S1Ps increases over time.	Additionally, long-term safety data from extension and observational trials were utilized in the Harms section to note whether any new safety signals emerged as compared to pivotal trial data.
6.	Infusion costs and capacity: We understand that ICER's focus is on ublituximab to provide pre-approval information to payers. Clinical advisors to the MS Coalition stated that the only reason they may switch patients to ublituximab is related to the shorter infusion time. Payers and integrated health systems may be interested in reducing infusion center costs or enhancing infusion center capacity. To that end, additional discussion related to infusion cost or capacity may be a relevant discussion point throughout the report.	In Table E15, we discuss the differences in infusion time for each of the infused agents. Further, we model additional costs as the number of infusions and the duration of infusion increases.
7.	Assumption: We conducted a scenario analysis where treatment stopped when a patient reached an EDSS of 7 or higher.  Clinical advisors disagreed with the assumption that EDSS 7 is an appropriate cutoff and suggested that EDSS 8.5 is a more reasonable assumption.	Our base-case analysis models a lifetime duration of treatment based on what we heard from patients and clinical experts and aligns well with what you suggest here. We modeled an earlier discontinuation (after EDSS 7) only as a scenario analysis.
8.	Assumption: Trial-reported discontinuation will be annualized and applied over the first two years after initiating treatment. Discontinuation after two years is assumed to be related to serious adverse events only and will not vary by treatment.  In the draft report, ICER assumes patients who discontinue initial therapy will switch to a comparable alternative treatment and continue the second course of therapy until death. ICER further assumes discontinuation after two years to be "related to serious adverse events only." These assumptions are not reflective of the heterogeneity of actual MS treatment pathways. Many patients with MS will switch treatment more than once and may discontinue treatment beyond the first two years for reasons other than serious adverse events, such as loss of efficacy or reduced tolerability over time.  In general, we do not believe relying on trial-reported discontinuation appropriately accounts for the impact of age and sex assigned at birth on treatment discontinuation. Furthermore, disease progression and response to medication may affect treatment discontinuation in older individuals since remyelination and regeneration of neurons decreases with age and longevity of disease. Additionally, patients may also discontinue treatment for family planning. Since PwMS are more likely to be female, and diagnosis typically occurs between the ages of 20 and 40, this factor is likely important when considering discontinuation. Since clinical trials are likely to exclude pregnant women or may become pregnant, insights into discontinuation due to pregnancy will not be captured in clinical trial data.	We agree that at the patient-level discontinuation patterns vary dramatically, but the model's primary goal is to identify a fair price range and that is done at a population level.

	<p>Furthermore, disease progression and response to medication may affect treatment discontinuation in older age (~ after age 50) since disease longevity and chronic inflammation inhibit remyelination capacity. We recommend conducting an analysis that considers the potential impact of age on discontinuation rates.</p>	
9.	<p>Assumption: If a patient discontinued the initial therapy (either intervention or comparator), they transitioned to a subsequent treatment with cost and effectiveness similar to that of the market leading monoclonal antibody. We believe this assumption does not accurately reflect real-world treatment patterns and identify two major conflicts with this assumption:</p> <p>First, many patients discontinue treatment and refrain from any future treatment for a multitude of reasons. Reasons for discontinuing DMTs, include medication intolerance; lack of improvement; adverse events, disease progression, and mental health. Among those who discontinued a DMT, treatment was restarted by approximately half of patients after a mean of 0.93 (1.6) years. Hua et al. (2019) observed in older populations (60+), 29.7% of patients discontinued any treatment of DMT, and additionally attributed stable disease, comorbidities, and cost as justifications.<sup>8</sup> Among these discontinuers, only 10.7% later re-initiated DMT use.</p> <p>Second, individuals living with MS will try many treatments throughout their disease progression. In a Swiss population study on DMT usage, 26% of people with MS had tried several therapies. Clinical advisors to the MS Coalition also suggest that it is more likely that individual's subsequent DMT after dimethyl fumarate is the market-leading oral therapy.</p> <p>In addition, the model should address relapse and side-effect factors experienced by patients when they transition to different DMTs. Transitioning patients to a treatment basket will mask differences between treatments. For example, the same study by Bossart et al. identified that PwMS had vastly different responses to each therapy, with 9.7% of individuals taking natalizumab versus 56.7% of individuals taking dimethyl fumarate experiencing side effects.</p>	<p>We agree that the specific subsequent treatment will vary in the real world; however, our objective is not to recommend treatment sequences or evaluate the cost effectiveness of a specific treatment sequence. To achieve the objective of our analysis of estimating the cost effectiveness of a specific intervention, we held this subsequent treatment fixed to emphasize the potential differences in the initial treatment. Our approach standardized the treatment switch across the modeled arms (both the intervention and the comparator) and ensured the cost and effectiveness of the subsequent treatment did not drive the results. The subsequent treatment characteristics were varied in scenario analyses, and as can be observed by reviewing the results of the scenario analyses, so long as the subsequent treatment is consistent across the intervention and comparator, the subsequent treatment influences the findings very little. Rather the initial treatment drives the findings, which aligns with our intended objective.</p>
10.	<p>While exhaustive searches cannot, and should not, be conducted for every model parameter, the search processes used to populate key model parameters should be transparently reported and justified. This establishes that data sources have not been “serendipitously, opportunistically, or preferentially” identified. The ICER draft report does not document search processes for any model parameters used in its economic evaluation. This limits our confidence that the most appropriate sources of evidence have been identified and selected for use. Specific concerns regarding data inputs include:</p>	<p>We provided the model inputs to manufacturers, patient groups, and clinical experts in a preliminary model presentation. Inputs were also posted publicly in our model analysis plan. Stakeholder groups could provide feedback and alternative input sources for us to consider. If there are specific alternative sources you would recommend, we would have appreciated receiving that feedback with time for us to consider them in our revised analysis.</p>



	<ul style="list-style-type: none"> <li>• The equation used to calculate mortality multipliers used in the draft report is derived from values reported in Pokorski et al. 1997. This publication drew data from an earlier study, Sadovnik et al. 1992,3 conducted by the MS Society of Canada and followed patients in MS clinics from 1972 to 1985. These mortality multipliers may not reflect present day populations. For example, smoking status influences the risk of MS disease progression. The steady decline of cigarette smoking in recent decades could affect excess mortality due to MS.</li> <li>• A data source used to calculate secondary-progressive multiple sclerosis ARR and utilities was conducted among MS patients living in the United Kingdom between 1976-1980.</li> <li>• Annual probabilities of SAEs were estimated using clinical trial data. These may not accurately reflect real-world incidence of SAEs. Long-term safety or observational evidence should be used where available to estimate adverse event rates.</li> <li>• From the draft report, it is unclear whether the original source material for health-state utilities (HSUs) derived from other economic evaluations were evaluated for appropriate quality and relevance to this evaluation.</li> </ul> <p>Many of these inputs rely on data from the 1970s-80s and do not reflect the current or even recent standard of care. Ideally, more recent studies or inputs from real-world sources should be substituted for these model inputs. For example, clinical advisors to the MS Coalition note there is variation in how rituximab is dosed across settings (e.g., 1000mg every 6 months instead of 500 mg every 6 months as indicated in the draft report).</p>	
11.	In general, we are surprised that ICER does not adhere to research reporting conventions and include a “Limitations” section for each of the studies. While the NMA and cost-effectiveness analysis include a section on “Uncertainty and Controversies,” the budget impact analysis does not. Its’ absence raises concerns regarding transparency.	The following sentence is included within the budget impact section: “Identifying the appropriate eligible population for the potential budget impact analysis was challenged by the number of existing treatments available, the different types of DMTs available, whether or not a patient is currently on a DMT or is new to treatment with a DMT, and whether or not a patient is stable on their DMT if currently taking a DMT.”
12.	In the model validation section of the draft report, ICER states that data inputs were refined based on feedback from manufacturers, patient groups, and clinical experts “as appropriate.” This statement is vague and appears in many ICER reports. Transparent documentation regarding which data inputs were adjusted and to what degree would improve stakeholder confidence in ICER’s model validation process.	We report and publicly post the model inputs from our model analysis plan and in each iteration of our report. A review of the model inputs between these documents displays which inputs have changed. Further, with each version of the report, we include a paragraph of key changes made since the prior report.
13.	Please double check reference numbering throughout the report. We noted inconsistencies throughout the report, for instance, at the top of page 17, citation 39 regarding diroximel fumarate should reference citation 33.	These references have been revised as requested.

14.	On page ES1, there is a sentence stating that there was a review of the clinical effectiveness of oral and monoclonal antibody treatments that are considered first line DMTs. There was no reference cited for this statement.	This sentence is in reference to the current MS report.
15.	Page 1, paragraph 1 or 2: In your introduction, we recommend stating that people identifying as Hispanic appear to have an earlier onset of MS symptoms.	Thank you for this comment. We have added this to the introduction.
16.	Page 2, paragraph 2: Since ICER references ongoing discontinuation studies in the second half of the paragraph, we suggest also including references to the escalation vs. highly effective treatment trials (DELIVER-MS and TREAT-MS) in the first paragraph.	These references have been added as requested.
17.	On page 2, paragraph 2, it states that choice of initial therapy varies. Nowhere does it mention that insurance coverage in most instances, determines what DMT is prescribed for the patient. We know that Medicare and Medicaid (and no insurance) limit access to appropriate medications in many instances.	Thank you for this comment. We agree that insurance coverage is an important determinant DMT choice and have updated the report to include it in the Background and Patient Perspective sections.
18.	Table 3.2: Hypogammaglobulinemia should be listed as a known harm on the summary.	The Harms section has been updated to include the risk of hypogammaglobulinemia and its impact on vaccine administration.
19.	Page 23, paragraph 2: On page 20, ICER notes that disability progression is the outcome prioritized by many patients and clinicians. We recommend including this in the summary on page 23.	Thank you for this comment. In our Summary section we have now noted that our review focuses on the ARR and CDP outcomes.
20.	Diroximel fumarate is not a metabolite of dimethyl fumarate. It is a different drug, but like dimethyl fumarate, it is immediately metabolized to the active compound, monomethyl fumarate.	Please see response to Biogen #10 as this description has been corrected.
21.	<p>Voting Question: When making judgments of overall long-term value for money, what is the relative priority that should be given to any effective treatment for multiple sclerosis, on the basis of the following contextual considerations</p> <ul style="list-style-type: none"> <li>• Current response option: “Acuity of need for treatment of individual patients based on short-term risk of death or progression to permanent disability” <ul style="list-style-type: none"> <li>○ Comment: Short-term risk of death is not relevant to MS and DMPMLT treatments.</li> <li>○ Suggested modification: “Acuity of need for treatment of individual patients based on <del>short-term risk of death</del> or progression to permanent disability”</li> </ul> </li> <li>• Suggested additional response option: Likelihood of adherence due to factors like ease of treatment (route of administration and side effect profile), monitoring burden, excess costs not captured in drug prices (ex: monitoring costs, infusion costs)</li> </ul>	We use these statements across diseases and don’t make edits to fit any particular disease. Voters should interpret the “or” in the statement as it is intended.
22.	What are the relative effects of ublituximab versus dimethyl fumarate on the following outcomes that inform judgment of the overall long-term value for money of ublituximab?	We use these statements across diseases and do not tend to make edits to fit any particular disease. Side effects are an implied component of an ability to manage and sustain treatment.

	<ul style="list-style-type: none"> <li>• Current response option: Patients’ ability to manage and sustain treatment given the complexity of regimen</li> <li>• Suggested addition: Patients’ ability to manage and sustain treatment given the complexity of regimen <u>and tolerance of side effects</u></li> </ul>	
23.	<p>Finally, for understandability to individual patients who may be engaged or interested in the voting exercises, we encourage ICER to include brand names in addition to generic names.</p>	<p>Thank you for this suggestion. We’ve updated the voting questions to include brand names in addition to generic names.</p>

#	Comment	Response/Integration
<i>Other</i>		
<b>Partnership to Improve Patient Care</b>		
1.	<p>ICER's model should incorporate caregiver burden.</p> <p>This is a prime example of an assessment that would be better served with a model that captured the full societal perspective versus the pure health care perspective. MS is a degenerative disease that frequently requires a lot of time and energy from family caregivers. This reality should be depicted in any modeling on the value of treatments for MS.</p> <p>Although some people with MS continue to live independently and maintain a high quality of life, others require ongoing care and support. Often, family members and friends are required to deliver this support, taking on the role of informal caregivers. It is generally accepted that caring for MS patients has associations with losses in health-related quality of life and well-being. For example, one recent study found that MS caregivers had lower health-related QOL than non-caregivers, with 68% experiencing pathologic anxiety and 44% experiencing pathologic depression, using the Hospital Anxiety and Depression Scale. Objective burden is directly associated with the overall cost of caring, both in terms of economic cost and losses in productivity, and is consistent with the finding that caregiving for MS patients is associated with considerable economic burdens, even in a population with low levels of physical disability.</p> <p>The healthcare costs associated with the higher burden of caregivers in terms of stress and health-related quality of life are also inevitably borne by payers, so to exclude these values when modeling costs and outcomes for treatments of MS fails to paint a complete picture. ICER should include both caregiver healthcare costs and, if insisting on using QALYs, also include caregiver QALY loss in its calculations.</p> <p>NICE, which ICER leans heavily on for its approach to value assessment, has already included caregiver utility in its cost-effectiveness models for MS and other diseases with a similar impact on caregivers, like Alzheimer's and Parkinson's disease. It is also the recommended perspective for cost-effectiveness models of the 2nd panel on cost-effectiveness, and ISPOR. We would urge ICER to learn from these other organizations and incorporate caregiver utility in this model.</p>	<p>In our modified societal perspective analysis, we include costs for not only the primary caregiver but also the secondary caregiver. We include costs to the primary and secondary caregiver related to early retirement, absenteeism, presenteeism, and social productivity loss in volunteer work. We did not identify a suitable source that suggests caregiver quality of life significantly varies by EDSS score.</p>
2.	<p>ICER should incorporate health equity more fully in all of its assessments.</p> <p>ICER is clear in its report that some subpopulations, including African Americans, bear a larger burden of disease, possibly due to both differences in disease characteristics and disparities in access to treatment. Knowing this, ICER should acknowledge the role access to treatment can play in</p>	<p>We agree that health inequities are an important issue in our health care system, and particularly for MS patients. We have noted in our report where disparities exist and continue to work on developing methods to incorporate health equity more fully into our reports and into value assessment.</p>

	<p>advancing health equity and be clear when a treatment may not only improve the life of individual patients, but also has the potential to assist in addressing systematic health inequalities. ICER has stated that it understands its obligation to work with the entire ecosystem to advance health equity. In this mindset, it should evaluate the downstream effects of its decisions. Communities of color are at a disadvantage due to a century of underinvestment in solutions to diseases that predominantly affect them. By ignoring these effects, ICER perpetuates and unequal health system. PIPC urges ICER to take immediate action to incorporate a goal of greater health equity into its models.</p>	
<p>3.</p>	<p>PIPC encourages ICER to reevaluate its modeling choices to paint a more accurate picture of value to the patient.</p> <p>Multiple studies have shown that cost-effectiveness models that use the QALY discriminate against patients with chronic conditions and people with disabilities. There is widespread recognition that the use of the QALY is discriminatory. The National Council on Disability (NCD), an independent federal agency, concluded in a 2019 report that QALYs discriminate by placing a lower value on treatments which extend the lives of people with chronic illnesses and disabilities. NCD recommended that policymakers and insurers reject QALYs as a method of measuring value for medical treatments. PIPC encourages ICER to heed this advice and work to develop and use better, non-discriminatory metrics.</p> <p>In recent years within the academic community, there has also been a widespread questioning of several of the assumptions upon which standard cost utility analysis is built. This argument has been most prominent with respect to the reliance on the assumption that every unit of health gain is equal in value. In other words, a single unit of health generates the same utility whether that health is accrued to someone who is suffering considerable disease burden, or to someone who is suffering minimal disease burden. Several health technology assessment systems in Europe have backed away from direct use of strict cost-per-QALY estimates for this very reason, and incorporate the role of severity adjacent to the results to make a more context-relevant case for, or against, a new technology.</p> <p>A system of evaluation that treats therapeutic innovations in these disease spaces as of similar relative value for unit of health gain in less severe conditions is inherently unfair and harms those facing the greatest disease burden. Multiple studies have made this case. In fact, even NICE has recently stated it will start looking at expanding the set threshold for what is considered cost-effective.</p> <p>PIPC would encourage ICER to reevaluate its metric and modeling choices given ongoing research and understanding of how value assessments impact patients.</p>	<p>We appreciate the concerns about relying solely on QALYs. However, the QALY is not used in the assessment of the comparative net health benefit (more information on the ICER Evidence Rating Matrix may be found <a href="#">here</a>). Further, QALYs are also only one component of the value assessment. Specifically, many of the issues raised are captured in the Potential Other Benefits and Contextual Considerations section and represent important components of value assessment.</p>

<p>4.</p>	<p>PIPC encourages ICER to reassess its model inputs to create a more accurate model.</p> <p>For its modeling, ICER selected a linear interpolation of a mortality multiplier by EDSS from a study from 1997, instead of one taken from actual mortality data by EDSS from a real-world study published in three papers from 2018-2021. ICER provides two reasons for its choice of data set, neither of which are compelling as a reason to use the 1997 data set in favor of more recent real-world data.</p> <p>ICER says one reason it favored the 1997 mortality ratios is so that its model would be consistent with previous MS models, which relied on those same inputs. The systemic review ICER cites includes 127 studies, but over 60% of these were conducted before the 2018 paper was published.</p> <p>The second reason ICER gave for selecting the 1997 data over that from 2018 was that the mortality rates from the 2018 paper shown in EDSS stages 8 and 9 are exponentially greater than those shown in 4-7, which were, in turn, much greater than those from a 'linear interpolation' from the 1997 data. The reality is that the 2018 real world data paints a more realistic picture of disease progression. Very sick people tend to have exponentially higher mortality rates than moderately sick people – this should be a signal for validity, not a trigger for concern.</p>	<p>Thank you for providing references for more recent sources. One of the sources only reported the cause of death for patients with MS rather than reporting a standardized mortality ratio by EDSS state. The other sources did report a standardized mortality ratio by EDSS state, which is what the model requires, but there was no evidence to inform the standardized mortality ratio for EDSS less than 5. Most importantly, the studies also state that the estimates are “most applicable to patients with RRMS whose age is similar to the mean age in the corresponding EDSS band” rather than for EDSS alone, so the correlation with age is not accounted for in these estimates.</p>
<p><b>Paul Langley</b></p>		
<p>5.</p>	<p>Although unrecognized by ICER in the draft evidence report and the majority, if not all, commentators addressing multiple sclerosis PRO instrumentation, there is an acceptable instrument in multiple sclerosis to support empirically evaluable PRO claims; this is the Patient Reported Indices of Multiple Sclerosis (PRIMUS) questionnaire. Not surprisingly, PRIMUS was overlooked by ICER in the 2017 evidence report.</p> <p>The PRIMUS instrument was developed some 15 years ago and published in 2009. The genesis was what the authors perceived as the failings of existing PRO measures in multiple sclerosis, specifically the need for a holistic measure to gauge the impact of multiple sclerosis to go beyond impairment and activity. The decision was made to create a needs-based measure of QoL. At the same time the opportunity was taken to create scales of symptoms (impairment) and activity limitations as single attributes that could be used as measures for application in clinical trials.</p> <p>The PRIMUS instrument therefore comprises three scales: MS QoL, MS symptoms and MS activity limitations. The conceptual basis for the PRIMUS classification rests, for the symptom and activity limitation scales on the respective WHO classifications for impairment (physiological and anatomical) and activity limitations (capacity and</p>	<p>Thank you for the information regarding the PRIMUS instrument. Unfortunately, PRIMUS was not systematically collected in the pivotal clinical trials used to assess the clinical effectiveness of the DMTs reviewed in our report. Thus, we are unable to comment on the effect of DMTs on PRIMUS.</p>



performance) respectively. The PRIMUS QoL scale is based on the needs-fulfillment conceptual model, applying Rasch measurement for item selection and fitting to create an interval scale. All three measures take the patient voice as the relevant perspective.

The item content for all three scales was derived from intensive patient interviews designed to explore how multiple sclerosis impacted their lives. For our present purposes only the PRIMUS-QoL scale is relevant. In the case of the PRIMUS-QoL the interviews resulted in a selection of item pools for the scale with a final item pool selected. Item selection was intended to fit the Rasch model while maintaining face validity. PRIMUS also supports claims for construct validity given that the instrument is based on a model of the construct assessed and good reliability. The Rasch model captures both the difficulty of the item, expressed in the patient's own words, and the ability of patients to respond to that item as assessed by item responses. This yields a ranking of items with scores representing the extent to which QoL as needs fulfillment is met.

Obviously, as an interval scale the PRIMUS scale cannot support multiplication and the creation of QALYs. This may be remedied with more recent applications of a rule to translate dichotomous Rasch modelling to create a bounded ratio scale, but the emphasis is on value claims for response to therapy not imaginary lifetime claims which are intended to be helpful in providing approximate information. Unfortunately, these are just numbers and not information; we have no idea whether the ersatz claims are helpful or unhelpful, we will never know and by design we are not intended to know.

May I suggest you review the PRIMUS instrument and make note of it in your final evidence report and the role of Rasch or modern measurement theory to construct interval scales for response to therapy that follow well developed rules for translating subjective ordinal responses to an interval scale. This is, of course in marked contrast to your unsustainable belief in the ratio properties of multiattribute preference scores and the necessity of including these to drive lifetime imaginary cost-effectiveness claims. If you insist on ignoring Rasch measurement, and you are not alone as evidenced by the Drummond et al leading textbook, at least you should make a case for why you are rejecting modern measurement.