

November 11, 2022

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Re: Public comments on Draft Evidence Report

Biogen welcomes the opportunity to comment on the Institute for Clinical and Economic Review's (ICER) 2022 Assessment of Treatments for Multiple Sclerosis (MS). Biogen has been a pioneer in the science of combatting the complex and debilitating disability associated with MS since before 1996 when Avonex[®] was approved by the Food and Drug Administration (FDA), taking bold steps to transform the way we treat MS today. Given our understanding of the heterogeneity of MS, we are providing the following comments and recommendations on this ICER's Draft Evidence Report with the ultimate goal that health care professionals and patients have access to all treatments.

Each Disease Modifying Treatment (DMT) has an individual efficacy and safety profile

As already highlighted in prior comments to this class assessment, MS is a very complex autoimmune disease and with multiple DMTs that have different mechanisms of action (MOA).¹ Specificities of each DMT and their associated mechanisms of action are currently not sufficiently characterized or acknowledged in the draft evidence report: the monoclonal antibodies (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.

Reported drug costs are inconsistent across DMTs and could lead to non-informative conclusions.

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.

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.



Additionally, in the draft report monitoring resource utilization associated with each intervention hasn't been described. In reviewing the economic model, it is apparent 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^{2,3} and Biogen recommend to carefully reflect such monitoring costs in the economic evaluation to ensure a balanced comparison between interventions.

Quality of Life of patients on EDSS 8.0 to 9.5

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.⁴ 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 >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.⁴

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.

Choice of comparator and discontinuation pattern in the cost-effectiveness model do not provide information applicable in clinical practice

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, dimethyl fumarate (DMF), is an oral treatment that is generally considered a moderate-efficacy therapy and used primarily for patients with mild to moderate disease activity.^{5,6} 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.

Furthermore, the inclusion of rituximab is not appropriate. It is neither approved nor projected to be approved by the FDA or any regulatory agency for the use in patients with relapsing remitting multiple sclerosis (RRMS). We strongly object to the inclusion of rituximab in any indirect treatment comparison for RRMS.

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.



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.

The Draft Evidence Report Excludes Important Published Data on Patient-Relevant Outcomes and only partially recognizes the holistic societal implications of MS.

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.⁷ 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.

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 symptoms are not assessed for value analysis; some with proven significant improvement for patients. For example, sexual dysfunction,⁸ depression, fatigue,⁹ bladder and bowel control¹⁰ have all been areas of significant improvement with, for example, natalizumab.

Capturing the burden of such a complex and heterogeneous disease in an economic model analysis is challenging, and therefore modelling the benefit of treatments for this disease is likely to result in an incomplete exercise that underestimates the value of those treatments not only to people with MS but also to their caregivers. Biogen believes that a modeling approach in this disease should have a broader societal perspective in the primary analysis, instead of the proposed health care system perspective. Societal benefits include the impact to caregivers, productivity costs and other indirect costs that are significant in MS.⁴

Section, Page	Comment				
Background,	Ind, Table 1.1 is not accurate for MOA for Tecfidera (DMF) and Vumerity (DRF). They are				
Page 3	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				
	homoeostasis in response to oxidative and toxic insults. ¹¹ 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-kB) activity in vitro ¹² and inhibits T-cell activation in vitro in an Nrf2-independent				
	mechanism. ¹³ Moreover, DMF, but not MMF, blocks the expression of proinflammatory				
	cytokine interferon-alpha. ¹⁴ We recommend editing the table lines for Tecfidera and				
Vumerity to read 'Nrf2 activator and NF-kB inhibitor', rather than 'anti-oxida					
	such change is need for Bafiertam (MMF).				
Indirect	The current sentence 'Diroximel fumarate and monomethyl fumarate are active metabolites				
Evidence:	of dimethyl fumarate." Is scientifically inaccurate and should be revised. We suggest				
Ublituximab	ab replacing by the following statement: Enzymatic hydrolysis of both dimethyl fumarate				

Specific issues and recommendations (in order of appearance)



versus Other	and diroximel fumarate results in the active metabolite monomethyl fumarate.			
DMTs and				
Placebo, page				
8				
Harms of	The draft safety data could benefit from additional information. Other infections, beyond			
Monoclonal	PML, associated with other high efficacy treatments, are not recognized. Additionally, anti-			
Antibody	CD20 therapies have warnings associated with reduction in immunoglobulins. ² These			
DMTs, Page	therapies also have warnings for infants born to mothers taking these treatments in that the			
16	inadvertent infant B-cell depletion must be monitored and repleted before any live or live-			
	attenuated vaccinations can be given. ² We respectfully request that such information be			
	included and associated monitoring costs should be accurately captured in the cost-			
	effectiveness model as well.			
Harms of	The statement "Cases of PML are rare and are associated with three risk factors: prior use of			
Monoclonal	immunosuppressants, more than 24 months of natalizumab exposure, and presence of anti-			
Antibody	JCV antibodies" is not relevant for other MS DMTs. These risk factors have been			
DMTs, Page	determined and established in natalizumab-treated patients only. We recommend revising			
16	to "Cases of natalizumab-related PML are rare and are 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. ¹⁵			
Harms of	The statement "The risk of developing PML can be mitigated by testing for JCV in patients			
Monoclonal	on higher-risk drugs" is applicable only to Biogen's natalizumab (Tysabri) treated patients.			
Antibody	The anti-JCV antibody test should only be used for patients considering or taking Tysabri.			
DMTs, Page	This test is validated only for Tysabri; it is not validated for any other MS therapy. Tysabri's			
16	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".			
Harms of	The statement "Discontinuation of natalizumab is associated with increased risk of rebound			
Monoclonal	relapse rates" should be reviewed. While there may always be outliers, the return of disease			
Antibody	activity of patients treated with natalizumab has been examined in multiple studies. ^{10,17} The			
DMTs, Page	studies have shown that there was a return of disease activity similar to what was seen			
16	before natalizumab treatment when not appropriately transitioned onto another DMT.			
Harms of	We strongly disagree with the statement "Limited observational data on the use of			
Monoclonal	monoclonal antibody DMTs (natalizumab, ofatumumab, ocrelizumab) prior to conception or			
Antibody	during pregnancy suggests no increased risk of adverse outcomes". For these DMTs, the			
DMTs, page	currently approved prescribing information state that there are currently no adequate data on			
16	the developmental risk associated with use of these DMTs in pregnant woman. ^{2,3,13}			
	Observational studies do not provide enough information which would allow a claim of "no			
	increased risk". We recommend rewriting this statement as suggested above.			
Heterogeneity,	Within the Subgroup Analysis and Heterogeneity, we recommend that duration of disease is			
page 19	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. ¹⁵ 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 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. ¹⁸				
	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) ¹⁹ and BRAVO				
	(2014) ²⁰ The AFFIRM pivotal trial manuscript was published in 2006. Therefore, we				
	recommend mentioning this as a limitation to the analysis.				
3.3. Summary	"Short-term safety signals appear similar across the drugs, barring a black box warning of an				
and Comment,	elevated risk of PML with natalizumab, but there is no long-term safety data for ublituximab				
page 23	yet." We recommend revising to include that rituximab also has a black box warning				
	for PML, ²¹ "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."				
Assessment of	We kindly request a change to both Table D8. Study Design and Table D4. Risk of Bias				
Bias, page	Assessment, regarding the CONFIRM study design description and 'randomization				
D11 and D3	concerns', respectively. Both DEFINE and CONFIRM were randomized, double-blind,				
Evidence	placebo-controlled, Phase 3 clinical trials. ^{22,23} CONFIRM in addition to the placebo arm, did				
Tables, page	have a rater-blinded, active agent (glatiramer acetate) included as a reference comparator to				
D27	allow a relative benefit-risk assessment of DMF through comparison to the active-treatment				
	groups with the placebo group. ²¹ As these studies were nearly identical in design, their				
	designation should both read 'low' on this table.				

Summary

Biogen is a long-time leader in researching and developing MS therapies. Through our own research on comparative effectiveness and the value of our therapies, we have made recommendations to ensure that ICER's report of MS therapies represents a better comparative assessment of value. These recommendations include acknowledging each unique DMT MOA with its associated safety and efficacy, ensuring appropriate selection and reporting of costs associated with each treatment to enable a balanced interpretation of the results, expanding the perspective to include more real-world assessments of value and to incorporate caregiver burden.

Finally, there are inaccuracies and inconsistencies in ICER's draft evidence review of MS therapies which should be corrected in the final report. Without correction, the current review introduces significant heterogeneity and biases in comparative effectiveness influencing the assessment of value.

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Sr. Director, Biogen Global Value and Access, Multiple Sclerosis Franchise Lead



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Submitted via email: publiccomments@icer.org

November 10, 2022

RE: Draft Evidence Report titled "Oral and Monoclonal Antibody Treatments for Relapsing Forms of Multiple Sclerosis: Effectiveness and Value"

Dear ICER Review Committee,

Bristol Myers Squibb (BMS) appreciates the opportunity to comment on the clinical evaluation contained in the Institute for Clinical and Economic Review's (ICER) Draft Evidence Report titled "Oral and Monoclonal Antibody Treatments for Relapsing Forms of Multiple Sclerosis: Effectiveness and Value." BMS's mission is focused on the discovery, development and delivery of innovative medicines that help patients prevail over serious diseases, including multiple sclerosis (MS). We appreciate ICER's commitment to open dialogue and feedback and would like to recommend some additional considerations in the comprehensive evaluation of MS treatments.

Safely preventing disability is of critical importance to patients with MS, as well as their physicians and caregivers. Confirmed disability progression (CDP), the central measure of disability in this review, is based on the Expanded Disability Status Scale (EDSS), which focuses on physical function. However, as ICER acknowledges, both cognition and fatigue are also important markers of overall quality of life and disease progression. In a preliminary study among older patients with relapsing remitting MS (RRMS), fatigue was reported to be four times as likely among patients with versus without disease progression.¹ Another 10-year retrospective study among patients with RRMS found that patients with cognitive impairment at diagnosis had a three times higher rate of reaching EDSS of 4.0 and a two times higher rate of secondary progressive MS (SPMS) conversion compared to cognitively preserved patients.² Brain volume loss is also known to be associated with long-term worsening disability.³ In contrast, CDP has limited prognostic value for time to next EDSS progression, time to EDSS 6, and time to SPMS,⁴ and may overestimate the accumulation of irreversible disability as several studies have found up to half of patients who experience disability progression do not sustain the progression over the duration of follow-up.⁵⁻⁷ It is also important to patients that improvements in their disability status are achieved with minimal impact on safety.

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 a network meta-analysis (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.⁸⁻¹¹ 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, 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.

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.¹² 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.

In summary, 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.

Sincerely,

43

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November 11, 2022

Institute for Clinical and Economic Review (ICER) 2 Liberty Square Boston, MA 02109

Dear ICER Review Panel:

Genentech, a member of the Roche group, appreciates the opportunity to provide feedback on ICER's Draft Evidence Report: *Oral and Monoclonal Antibody Treatments for Relapsing Forms of Multiple Sclerosis: Effectiveness and Value* [1]. We are committed to engaging with ICER to support a final report that summarizes the existing evidence in an objective manner to facilitate appropriate discussion on the value of these important treatments for patients with relapsing forms of multiple sclerosis (MS).

We recognize the challenges of conducting an assessment of comparative effectiveness and costeffectiveness in a heterogeneous and evolving disease area with many treatment options, limited head-tohead 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.

We agree with ICER's stated limitations of the assessment within the Draft Evidence Report, and encourage ICER to provide added transparency to readers with more robust discussion of these challenges and resulting uncertainties. Additionally, we advise ICER to consider a value assessment that more accurately reflects clinical practice, as theoretical exercises of economic evaluation – including the use of hypothetical comparators – have limited application and may lead to negative consequences for patients.

As the Evidence Report is being finalized, we urge ICER to consider the following recommendations:

- 1) Revisit conclusions regarding the net health benefit (NHB) of ublituximab.
- 2) Remove the scenario analysis with the hypothetical biosimilar from the economic assessment.
- 3) Provide comprehensive discussion regarding the limitations of the network meta-analysis (NMA) conducted in the comparative clinical effectiveness assessment.
- 4) Modify assumptions in the economic assessment to better reflect clinical practice in MS.
- 5) Remove or revise the scenario analysis incorporating treatment effect on confirmed disability improvement (CDI) for the cost-effectiveness analysis (CEA).

We further expand on these recommendations with supporting rationale and implications below:

1. Revisit conclusions regarding the NHB of ublituximab.

Recommendation: Review and reconcile inconsistencies in the conclusions regarding ublituximab's NHB with findings for both annualized relapse rate (ARR) and confirmed disability progression (CDP) from the NMA, as well as ICER's previous reviews of investigational therapies.

Rationale: 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 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]."

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.

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 adverse events (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 [2,3]. 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.

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 people with MS (PwMS), their families, and the health system, it is critical that ICER presents a more comprehensive assessment of ublituximab's NHB.

2. Remove the scenario analysis with the hypothetical biosimilar from the economic assessment.

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.

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.

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 relapsing-remitting MS (RRMS) patients, and rituximab-treated patients experienced significantly higher ARRs (rate ratio 1.8 (95% CI 1.4-2.4), p<0.01) compared with ocrelizumab [4].

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 [5]. The methods and rationale for use of a '*hypothetical*' comparator in this review are also absent from acknowledged best practices for health economic modeling [6,7]. Consequently, the proposed scenario analysis will fail to meet the goals of health technology assessment (HTA), which are to generate relevant evidence and inform key decision-makers about the dissemination, use, and reimbursement of available health technologies based on <u>currently available or soon to be available real-world treatment</u> choices.

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.

3. Provide comprehensive discussion regarding the limitations of the NMA conducted in the comparative clinical effectiveness assessment.

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.

Rationale: ICER's use of an NMA helps to support a simplified comparison of efficacy across diseasemodifying therapies (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 [2]. The current approach, assumptions, and sources used in ICER's NMA produced findings that are generally consistent with the existing body of evidence on comparative effectiveness [8-12]. 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.

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.

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.

4. Modify assumptions in the economic assessment to better reflect clinical practice in MS.

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:

(1) 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).



(2) 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 mechanism of action (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:

- 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.
- Individuals who initiate and discontinue natalizumab 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 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.

- <u>Discontinuation beyond two years</u>: 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 [13-16].
- <u>Reasons for discontinuation beyond safety</u>: 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 [15,17-20]. Additionally, the use of DMTs declines with increases in EDSS scores, older age, and longer disease duration, particularly among patients with SPMS [13,15,21-23]. 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 [24].

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" [24]. 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 discontinuation of the first-line treatment, patients transition to best supportive care to solely assess the value of first-line treatment in modeling exercises [25-28].

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.

5. Remove or revise the scenario analysis incorporating treatment effect on CDI for the CEA.

Recommendation: Remove Scenario Analysis 7 in entirety, or revise Scenario Analysis 7 to estimate the impact of incorporating treatment-specific CDI for <u>all</u> interventions of interest.

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.

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.

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.

In conclusion, Genentech provides the recommendations above to support a robust and objective assessment that more comprehensively reflects current clinical practice and the totality of evidence in this space. While we feel strongly that choice of treatment should be left to PwMS and their healthcare providers given individual patient needs and preferences, we are also confident in the value that Ocrevus brings to PwMS since its approval in 2017. The value of Ocrevus demonstrated in clinical trials is further underscored by long-term clinical experience and real-world data, and we remain committed to improving the lives of PwMS by continuing our investment in research.

We thank you again for the opportunity to provide input and welcome any questions or concerns.

Sincerely,



Jennifer Whiteley, EdD, MSc, MA Head of Evidence for Access OMNI Genentech, U.S. Medical Affairs



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November 11, 2022

Steven D. Pearson, MD, MSc President Institute for Clinical and Economic Review Two Liberty Square, Ninth Floor Boston, MA 02109

Re: Comments on "Oral and Monoclonal Antibody Treatments for Relapsing Forms of Multiple Sclerosis: Effectiveness and Value Draft Evidence Report" dated October 17, 2022

Dear Dr. Pearson:

Novartis Pharmaceuticals Corporation (Novartis) appreciates the opportunity to provide responses to the Institute of Clinical and Economic Review's (ICER) Draft Evidence Report for the assessment of treatments for Multiple Sclerosis (MS).

Executive Summary

In brief, Novartis recommends that ICER:

- 1. Consider a more comprehensive and high-quality evidence base to inform network metaanalyses (NMA).
- 2. Use reanalyzed confirmed disability progression (CDP) data from ASCELPIOS I/II to reduce bias in modelled indirect comparative efficacy estimates.
- 3. Acknowledge more prominently the methodological limitations of NMA in addressing crosstrial heterogeneity in patient population characteristics and its implications for comparing efficacy outcomes across trials.
- 4. Use drug cost estimates that more accurately account for real-world mark-ups on infusible DMTs.
- 5. Incorporate indirect treatment costs into the base-case analysis.

The remainder of this letter provides a more detailed discussion of these points.

1. Novartis recommends that ICER consider a more comprehensive and high-quality evidence base to inform network meta-analyses.

A key advantage of a network meta-analysis (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 multiple sclerosis (MS) space, there are many randomized controlled trials (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

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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.

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.

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.

2. Novartis recommends that ICER use reanalyzed CDP data from ASCELPIOS I/II to reduce bias in modelled indirect comparative efficacy estimates.

The definition of confirmed disability progression (CDP) has several components, including increase in Expanded Disability Status Scale (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 Appendix D (NMA Limitations) of the draft ICER report, there were variations in the definition of confirmed disability progression (CDP) across trials included in the NMAs.

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 for Ascuted 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).

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

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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.

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.

3. 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.

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 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.

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 of atumumab and ocrelizumab. Leveraging patient-level data for of atumumab, 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 of atumumab 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 of atumumab 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 of atumumab. These findings exemplify the limitations of NMA in addressing potential bias introduced by cross-trial heterogeneity.

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).

4. Novartis recommends that ICER use drug cost estimates that more accurately account for real-world mark-ups on infusible DMTs.

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 intravenous (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).

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.

5. Novartis recommends that ICER incorporate indirect treatment costs into the base-case analysis.

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 absenteeismrelated 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.

Furthermore, we suggest that ICER include caregiver time cost and disutility into the costeffectiveness 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).

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.

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Sincerely,

A F. G. adkari

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Institute for Clinical and Economic Review Two Liberty Square, Ninth Floor Boston, MA 02109 Submitted via email: publiccomments@icer.org **RE: Draft Evidence Report for the Assessment of "Treatments for Multiple Sclerosis: Effectiveness and Value"**

November 11, 2022

Dear ICER Review Team,

Sanofi appreciates the opportunity to provide comments on ICER's draft evidence report titled "*Treatments for Multiple Sclerosis: Effectiveness and Value*" in which teriflunomide (AUBAGIO®) is included.

Teriflunomide is approved in the US for the treatment of relapsing forms of multiple sclerosis (MS), including clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults.¹

Despite the availability of multiple treatments with different mechanisms of action and routes of administration, no treatment has been proven to halt or completely reverse the progression of MS. This fact, coupled with the inherent heterogeneity of disease course and treatment response across patients living with MS, validates the need for new treatment options for this devasting disease.

Given the remaining unmet need for effective treatments that meet the needs of a diverse patient population, we would also like to stress the importance of ensuring that patients and providers have access to all treatment options for MS. We encourage ICER, throughout its revised evidence report and particularly in future discussions at the policy roundtable, to reiterate the need for better treatments and to ensure that the findings of this report are not misused to enact access barriers for patients living with MS and the physicians who care for them.

KEY OBSERVATIONS

Sanofi encourages ICER to include novel endpoints, such as confirmed disability improvement (CDI) as part of the network meta-analysis. Despite acknowledging the importance of a broader set of endpoints in the revised scoping document², ICER's indirect treatment comparisons between the interventions of interest is limited to confirmed disability progression (CDP) and reductions in annualized relapse rate (ARR). Multiple clinical trials^{3,4,5,6}, have reported CDI results, and we respectfully request that ICER discuss whether it conducted a feasibility

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analysis of conducting the Network Meta-Analyses (NMA) using CDI and clarify to what extent it would be possible to conduct any comparisons between the interventions of interest.

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 annualized relapse rate (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.

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 globally⁷. During the review process, Sanofi also provided relevant publications, substantiating teriflunomide's real world effectiveness^{8,9,10,11,12,13}. 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.

Sanofi recommends more transparency on ICER's choice of NMA trial network to derive the relative risk (RR) of disease progression used in the costeffectiveness 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.

Sanofi believes that the report can benefit from greater clarity on the treatment benefit assumptions once patients have transitioned to secondary progressive multiple sclerosis (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 would also persist during the SPMS phase of the condition. It should be noted that natalizumab¹⁴, ocrelizumab,¹⁵ and ofatumumab's¹⁶ 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.

Page	Issue	Suggestions for Text Changes or Comments
E7	The baseline distribution of patients in Table E2 of the report only refers to RRMS.	Comment: The focus of the analysis is on "relapsing forms of MS", which should include clinically isolated syndrome (CIS), Relapsing-remitting Multiple Sclerosis (RRMS) and SPMS. The baseline distributions by EDSS score in Table TBD would suggest that only RRMS patients are included in the analysis.
		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.
E20	The economic model uses the same cost of relapse data ¹⁷ from the 2017 ICER assessment of MS treatments despite the availability of more recent sources.	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.
		Recommendation: Please update cost of relapse estimates based on more recent sources, such as Parisé <i>et al</i> ¹⁸ or Nicolas <i>et al</i> ^{,19}
E19	The economic model uses the cost generic DMF rather than a blended price of branded and generic DMF as it occurs in practice.	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.

DETAILED COMMENTS AND RECOMMENDATIONS

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Recommendation	
Please adjust the co	st of DMF to reflect
its actual use in pra	ctice by using a
blend of branded TE	CFIDERA and
generic DMF pricing	. There is precedent
for considering the	price erosion of a
generic in light of th	e continued
utilization of some b	pranded product ²⁰ ,
which could help inf	orm the cost of DMF
assumption or a sim	ple blended price of
generic weighted by	actual utilization
could be considered	

We appreciate the opportunity to be involved in this review and look forward to a continued dialogue with ICER.

Fight

Kyle Hvidsten Vice President Global Health Economics & Value Assessment Sanofi

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- ¹⁴ https://www.tysabri.com/content/dam/commercial/tysabri/pat/en_us/pdf/tysabri_prescribing_information.pdf
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¹ https://products.sanofi.us/Aubagio/aubagio.html

² https://icer.org/wp-content/uploads/2022/04/ICER_MS_Revised-Scope_052722.pdf



November 11, 2022

Steven D. Pearson, MD, MSc Institute for Clinical and Economic Review (ICER) 14 Beacon Street, 8th Floor Boston, Massachusetts 02108

RE: ICER's Draft Evidence Report for Relapsing Forms of Multiple Sclerosis

Dear Dr. Pearson:

TG Therapeutics is committed to developing novel treatment options for patients with b-cell diseases, including multiple sclerosis (MS), that improve patient outcomes. Our investigational therapy, ublituximab, is currently undergoing review by the US Food and Drug Administration (FDA) and has an expected Prescription Drug User Fee Act (PDUFA) date of December 28, 2022.

Ublituximab, a novel intravenously administered anti-CD20 monoclonal antibody, will add significant value to patients with relapsing forms of MS (RMS). In its two pivotal randomized controlled trials, ublituximab resulted in significant reductions in the annualized relapse rates (ARR) compared to teriflunomide [1]. Additionally, ublituximab may be associated with improved patient convenience based on a 1-hour infusion following the initial dose [2,3]. Healthcare providers (HCPs) increasingly agree that starting with a high-efficacy treatment earlier in disease course results in greater benefits in the short- and long-terms [4]. As such, ublituximab has a strong position in the class of high-efficacy monoclonal antibody treatments, and we look forward to bringing this important therapeutic option to market for patients with RMS.

TG Therapeutics acknowledges ICER's role in advancing the discussion of value across the US healthcare system and the stated aim of its draft evidence report (DER) to evaluate the health and economic outcomes of treatments for RMS. Below please find highlights of our comments to the DER along with further clarification for each of our comments in the subsequent section. We encourage ICER to consider these points to ensure that the final evidence report is fully representative of the current treatment landscape.

Highlights of TG Therapeutics' Comments

- (1) Limitations of the current assessment should be clearly stated in the summary and main body of the report
- (2) A balanced narrative of all monoclonal antibodies should be provided, particularly within the executive summary
- (3) Only interventions and comparators that have, or are currently seeking, FDA-approved indications in MS should be included
- (4) Adjustments regarding biosimilars should be made in the economic modeling analyses



Detailed TG Comments

(1) Limitations of the current assessment should be clearly stated in the summary and main body of the report

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.

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.

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 cost-effectiveness (CE) of ocrelizumab and ozanimod.

Limitation 2: *Different definitions of CDP and varying proportion of patients who received prior DMT impact the applicability of results.*

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.

Limitation 3: *Disability progression data from the respective pivotal trials raise concerns about the key drivers of the CE analysis.*

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.

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.*

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 [5,6]. 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.

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 [7]. 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 [7]. 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 EDSS stages as opposed to reserving this assumption for a scenario analysis.

Recommendation: ICER should highlight the above limitations in the appropriate sections within the summary and main body of the report so that their impact is transparent and not overlooked by those who do not review the supplemental pages.



(2) A balanced narrative of all monoclonal antibodies should be provided

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.

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.

(3) Only interventions and comparators that have, or are currently seeking, FDA-approved indications in MS should be included

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 offlabel 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 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.

Recommendation: ICER should remove rituximab from the comparative clinical effectiveness evaluation for the reasons stated above.

(4) Adjustments regarding biosimilars should be made in the economic modeling analyses

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).

Recommendation: ICER should remove the hypothetical monoclonal antibody biosimilar scenario analysis in the CE analysis and budget impact assessment for the reasons stated above.

Closing Remarks

Multiple sclerosis is a debilitating and progressive disease affecting a heterogeneous patient population. Clinical experts agree that earlier treatment with high-efficacy monoclonal antibodies has the potential to improve clinical outcomes, avoid further or future disability, and improve quality of life [4,7]. TG Therapeutics is committed to partnering across the healthcare system to support a heterogeneous population of patients with MS in accessing individualized approaches to patient care management. The recommendations made above are based on the strength of clinical evidence and the industry's reporting standards. We encourage ICER to consider these recommendations in the revised and final evidence reports.

Sincerely,

William Rose Executive Director, Access Marketing & HEOR william.rose@tgtxinc.com



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Appendix.

Table A1. Confirmed Disability Progression Definitions across Trials Included in NMA

Disability Progression Definition	Trial(s)
Baseline EDSS ≤5.5: Increase in EDSS of ≥1.0 points sustained for 3/6 months Baseline EDSS >5.5: Increase in EDSS of ≥0.5 points sustained for 3/6 months	ULTIMATE I and II, TRANSFORMS, FREEDOMS I, OPERA I and II, TEMSO, TOWER
Baseline EDSS 0: Increase in EDSS of ≥1.5 points sustained for 3/6 months Baseline EDSS 1.0-5.0: Increase in EDSS of ≥1.0 points sustained for 3/6 months Baseline EDSS >5.5: Increase in EDSS of ≥0.5 points sustained for 3/6 months	ASCLEPIOS I and II, OPTIMUM
Baseline EDSS ≤5.0: Increase in EDSS of ≥1.0 points sustained for 3/6 months Baseline EDSS >5.0: Increase in EDSS of ≥0.5 points sustained for 3/6 months	FREEDOMS II
Baseline EDSS 0: Increase in EDSS of ≥1.5 points sustained for 3/6 months Baseline EDSS ≥1.0: Increase in EDSS of ≥1.0 points sustained for 3/6 months	AFFIRM, CONFIRM, DEFINE
Baseline EDSS 0.0-5.0: Increase in EDSS of ≥1.0 points sustained for 3/6 months	SUNBEAM and RADIANCE
Baseline EDSS 0.0-5.0: Increase in EDSS of ≥1.0 points sustained for 3/6 months Baseline EDSS 5.5: Increase in EDSS of ≥0.5 points sustained for 3/6 months	BRAVO
Baseline EDSS 0: Increase in EDSS of ≥1.5 points sustained for 6 months Baseline EDSS 0.5-4.5: Increase in EDSS of ≥1.0 points sustained for 6 months Baseline EDSS >5.0: Increase in EDSS of ≥0.5 points sustained for 6 months	REGARD
Baseline EDSS 0: Increase in EDSS of ≥1.5 points sustained for 6 months Baseline EDSS ≥1.0: Increase in EDSS of ≥1.0 points sustained for 6 months	RIFUND-MS

EDSS: Expanded Disability Status Scale

Confirmed disability progression for EVIDENCE was not reported.

TENERE and HERMES did not report on confirmed disability progression, so it was not applicable.

November 11, 2022

Institute for Clinical and Economic Review

RE: ICER's "Oral and Monoclonal Antibody Treatments for Relapsing Forms of Multiple Sclerosis: Effectiveness and Value" draft evidence report

On behalf of the Multiple Sclerosis Coalition (MSC), a 501 (c) 3 network of nine independent MS organizations, thank you for the opportunity to comment on ICER's "Oral and Monoclonal Antibody Treatments for Relapsing Forms of Multiple Sclerosis: Effectiveness and Value" draft evidence report. We thank ICER's staff for addressing several of our comments on an early version of the draft report.

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:

- As a highly heterogenous 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.
- Several generic DMTs are expected to become available in the near future
- The opaque pricing system, including various discounts and rebates in the current market leave a great deal of uncertainty in the results
- There is a lack of diversity across clinical trial populations and the findings may not be generalizable to all PwMS

We recommend ICER consider including these considerations throughout the report. Specific suggestions to better reflect clinical practice and communicate uncertainty are described below.

We are concerned that the language and visuals reporting results of the network meta-analysis (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.

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.

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.¹ 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.²

- 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.
- **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 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.
- **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..

Assumptions in the Economic Evaluation

<u>Assumption/Rationale</u>: 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.

<u>Assumption</u>: 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.^{3,4} 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. Furthermore, disease progression and response to medication may affect treatment discontinuation in older age (~ after age 50)⁵ since disease longevity and chronic inflammation inhibit remyelination capacity.^{3,4} We recommend conducting an analysis that considers the potential impact of age on discontinuation rates.

<u>Assumption</u>: 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:

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.^{6,7} 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.⁸ Among these discontinuers, only 10.7% later re-initiated DMT use.

Second, individuals living with MS will try many treatments throughout their disease progression.⁹ In a Swiss population study on DMT usage, 26% of people with MS had tried several therapies.¹⁰ 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.

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.

Model Parameters & Transparency Regarding Limitations

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.¹ 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:

• The equation used to calculate mortality multipliers used in the draft report is derived from values reported in Pokorski et al. 1997.² 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.

- A data source used to calculate secondary-progressive multiple sclerosis annualized relapse rate (ARR) and utilities was conducted among MS patients living in the United Kingdom between 1976-1980.⁴
- Annual probabilities of serious adverse events (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.
- 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.⁵

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).

As noted in the draft evidence report, the EDSS does not sufficiently capture this complexity and multidimensionality. While ICER acknowledged this draft report, it is unclear what efforts have been made to include patient-important outcomes in the model.

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.

Model validation

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.

Other Comments & Specific Recommendations

- References: 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.
- 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.
- 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.¹¹

- 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.
- 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.
- Table 3.2: hypogammaglobulinemia should be listed as a known harm on the summary
- 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.
- 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.

Draft Voting Questions

<u>Voting Question:</u> 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

- <u>Current response option</u>: "Acuity of need for treatment of individual patients based on shortterm risk of death or progression to permanent disability"
 - <u>Comment:</u> Short-term risk of death is not relevant to MS and DMT treatments.
 - <u>Suggested modification</u>: "Acuity of need for treatment of individual patients based on short-term risk of death or progression to permanent disability"
- <u>Suggested additional response option:</u> 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)

<u>Voting Question</u>: 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?

- <u>Current response option</u>: Patients' ability to manage and sustain treatment given the complexity of regimen
- **Suggested addition:** Patients' ability to manage and sustain treatment given the complexity of regimen <u>and tolerance of side effects</u>

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.

The Coalition looks forward to continued engagement with ICER throughout the review process.

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- 3. Neumann B, Segel M, Chalut KJ, Franklin RJ. Remyelination and ageing: Reversing the ravages of time. *Mult Scler J*. 2019;25(14):1835-1841. doi:10.1177/1352458519884006
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November 11, 2022

Dr. Steven D. Pearson President Institute for Clinical and Economic Review Two Liberty Square, Ninth Floor Boston, MA 02109

Dear Dr. Pearson:

The Partnership to Improve Patient Care (PIPC) appreciates the opportunity to provide feedback on ICER's assessment of oral and monoclonal antibody treatments for relapsing forms of Multiple Sclerosis (MS).

MS symptoms can be unpredictable and highly individual. Of the available treatments, side effects also vary and, in some, can be severe. It is important that patients and providers have good information from which to make a decision as to which treatment is best for each patient.

PIPC asks ICER to consider the following comments.

ICER's model should incorporate caregiver burden.

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.

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.^{1,2} It is generally accepted that caring for MS patients has associations with losses in health-related quality of life and well-being.³ 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 pathological depression, using the Hospital Anxiety and Depression Scale.⁴ 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

¹ Bayen E, Papeix C, Pradat-Diehl P, Lubetzki C, Joël M. Patterns of objective and subjective burden of informal caregivers in multiple sclerosis. Behav Neurol. 2015;2015:1-10.

² Katsavos S, Artemiadis AK, Zacharis M, Argyrou P, Theotoka I, Chrysovitsanou C, et al. Predicting caregiving status and caregivers' burden in multiple sclerosis. A short report. Neurol Res. 2017;39(1):13-5.

³ Opara J, Brola W. Quality of life and burden in caregivers of multiple sclerosis patients. Physiotherapy and Health Activity. 2018;25(1):9-16

⁴ Giordano A, Cimino V, Campanella A, Morone G, Fusco A, Farinotti M, et al. Low quality of life and psychological wellbeing contrast with moderate perceived burden in carers of people with severe multiple sclerosis. J Neurol Sci. 2016;366:139-45.



caregiving for MS patients is associated with considerable economic burdens, even in a population with low levels of physical disability.⁵

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. 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.⁶ It is also the recommended perspective for cost-effectiveness models of the 2nd panel on cost-effectiveness⁷, and ISPOR.⁸ We would urge ICER to learn from these other organizations and incorporate caregiver utility in this model.

ICER should incorporate health equity more fully in all of its assessments.

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.^{9,10} Knowing this, ICER should acknowledge the role access to treatment can play in 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.

PIPC encourages ICER to reevaluate its modeling choices to paint a more accurate picture of value to the patient.

⁵ García-Domínguez JM, Maurino J, Martínez-Ginés ML, Carmona O, Caminero AB, Medrano N, et al. Economic burden of multiple sclerosis in a population with low physical disability. BMC Public Health. 2019;19(1):609.

⁶ Afentou N, Jarl J, Gerdtham UG, Saha S. Economic evaluation of interventions in Parkinson's disease: a systematic literature review. Movement disorders clinical practice. 2019 Apr;6(4):282-90.

⁷ Sanders GD, Neumann PJ, Basu A, Brock DW, Feeny D, Krahn M, Kuntz KM, Meltzer DO, Owens DK, Prosser LA, Salomon JA. Recommendations for conduct, methodological practices, and reporting of cost-effectiveness analyses: second panel on cost-effectiveness in health and medicine. Jama. 2016 Sep 13;316(10):1093-103.

⁸ Garrison Jr LP, Mansley EC, Abbott III TA, Bresnahan BW, Hay JW, Smeeding J. Good research practices for measuring drug costs in cost-effectiveness analyses: a societal perspective: the ispor drug cost task force report—Part II. Value in Health. 2010 Jan;13(1):8-13. ⁹ Roddam H, Rog D, Janssen J, Wilson N, Cross L, Olajide O, Dey P. Inequalities in access to health and social care among adults with multiple sclerosis: A scoping review of the literature. Multiple sclerosis and related disorders. 2019 Feb 1;28:290-304.

¹⁰ Marrie RA, Elliott L, Marriott J, et al. Effect of comorbidity on mortality in multiple sclerosis. *Neurology*. 2015;85(3):240-247.



Multiple studies have shown that cost-effectiveness models that use the quality-adjusted life year (QALY) discriminate against patients with chronic conditions¹¹ and people with disabilities.¹² 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.¹³ PIPC encourages ICER to heed this advice and work to develop and use better, non-discriminatory metrics.

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.¹⁴ This argument has been most prominent with respect to the reliance on the assumption that every unit of health gain is equal in value.¹⁵ 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.¹⁶ 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.^{17,18}

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 studies¹⁹ have made this case.^{20,21} In fact, even NICE has recently stated it will start looking at expanding the set threshold for what is considered cost-effective. PIPC would encourage ICER to reevaluate its metric and modeling choices given ongoing research and understanding of how value assessments impact patients.

PIPC encourages ICER to reassess its model inputs to create a more accurate model.

¹¹ Paulden M. Recent amendments to NICE's value-based assessment of health technologies: implicitly inequitable?. Expert review of pharmacoeconomics & outcomes research. 2017 May 4;17(3):239-42.

¹² Nord E, Pinto JL, Richardson J, Menzel P, Ubel P. Incorporating societal concerns for fairness in numerical valuations of health programmes. Health economics. 1999 Feb;8(1):25-39.

¹³ https://www.ncd.gov/sites/default/files/NCD_Quality_Adjusted_Life_Report_508.pdf

¹⁴ Beresniak A, Medina-Lara A, Auray JP, De Wever A, Praet JC, Tarricone R, Torbica A, Dupont D, Lamure M, Duru G. Validation of the underlying assumptions of the quality-adjusted life-years outcome: results from the ECHOUTCOME European project. Pharmacoeconomics. 2015 Jan 1:33(1):61-9.

¹⁵ Sund B, Svensson M. Estimating a constant WTP for a QALY—a mission impossible? The European Journal of Health Economics. 2018 Jul:19(6):871-80.

¹⁶ MacKillop E, Sheard S. Quantifying life: understanding the history of quality-adjusted life-years (QALYs). Social Science & Medicine. 2018 Aug 1;211:359-66.

¹⁷ Barra, M. and K. Rand-Hendriksen, A missing cornerstone in the Norwegian Priority Commission's weighting scheme–Sub-treatment balancedness is a necessary property for priority setting criteria. Nordic Journal of Health Economics, 2016. 4(2): p. pp. 8-23.

¹⁸ Swedish Parliamentary Priorities Commission, Priorities in health care: ethics, economy, implementation. 1995, Stockholm: Swedish Government.

¹⁹ Shiroiwa, T., et al., WTP for a QALY and health states: More money for severe health states? Cost Effectiveness and Resource Allocation, 2013. 11(1): p. 22.

²⁰ Lancsar, E., et al., *Deriving distributional weights for QALYs through discrete choice experiments*. Journal of health economics, 2011. **30**(2): p. 466-478

²¹ Richardson, J., A. Iezzi, and A. Maxwell, How important is severity for the evaluation of health services: new evidence using the relative social willingness to pay instrument. The European Journal of Health Economics, 2017. 18(6): p. 671-683.



For its modeling, ICER selected a linear interpolation of a mortality multiplier by Expanded Disability Status Scale (EDSS) from a study from 1997,²² instead of one taken from actual mortality data by EDSS from a real world study published in three papers from 2018-2021.^{23,24,25} 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.

ICER says one reason it favored the 1997 mortality rations is so that is model would be consistent with previous MS models, which relied on those same inputs. The systemic review ICER sites includes 127 studies, but over 60% of these were conducted before the 2018 paper was published.

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.

Conclusion

PIPC encourages ICER to reassess its modeling choices. Making some changes to the model including the incorporation of caregiver burden and reliance on real world data where available would create a more accurate picture of value of the treatment to patients.

Sincerely,

T_ Coelho

Tony Coelho Chairman Partnership to Improve Patient Care

²² Pokorski RJ. Pokorski RJ. Long-term survival experience of patients with multiple sclerosis. *J Insur* Med. 1997;29(2):101-106.

²³ Harding K, Anderson V, Williams O, Willis M, Butterworth S, Tallantyre E, Joseph F, Wardle M, Pickersgill T. Robertson N. A contemporary study of mortality in the multiple sclerosis population of south east Wales. Multiple sclerosis and related disorders. 2018 Oct 1;25:186-91.

²⁴ Harding K, Zhu F, Alotaibi M, Duggan T, Tremlett H, Kingwell E. Multiple cause of death analysis in multiple sclerosis: A population-based study. Neurology. 2020 Feb 25;94(8):e820-9.

²⁵ Walz L, Brooks JC, Shavelle RM, Robertson N, Harding KE. Life expectancy in multiple sclerosis by EDSS score. Multiple Sclerosis and Related Disorders. 2022 Oct 5:104219.

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Dr S D Pearson President Institute for Clinical and Economic Review Two Liberty Square, 9th Floor BOSTON MA 02109

8 November 2022

My dear Dr Pearson

PUBLIC COMMENT: ORAL AND MONOCLONAL ANTIBODY TREATMENTS FOR RELAPSING FORMS OF MULTIPLE SCLEROSIS: EFFECTIVENESS AND VALUE

I refer to your recently released draft evidence report for Oral and Monoclonal Antibody Treatments for Relapsing Forms of Multiple Sclerosis: Effectiveness and Value ¹

As you will no doubt recall, you are aware of my concerns that the ICER reference case framework for value assessment, the creation of assumption driven imaginary claims fails to meet the standards of normal science². That is, given the standards for credibility of claims, empirical evaluation and replication, that distinguish science from pseudoscience, you persist in creating these cost-effectiveness models when it is quite clear that they have no validity. Your reports for modeled claims, many of which are produced by expert academic groups, lack credibility in the claims made for the value of products; they cannot be evaluated empirically nor can the claims be replicated. Your models also violate the fundamental axioms of Rasch or modern measurement theory in confusing ordinal scales with interval and ratio scales ^{3 4}. While you might view your reports and the application of lifetime incremental cost-per-QALY calculations and the application of cost-per-QALY thresholds as the state of the art in health technology assessment, the problem is that the entire exercise is essentially a waste of time ⁵. This has been detailed in a recent publication in *F1000Research* which has addressed the manifest deficiencies in the CHEERS 22 guidance for constructing imaginary worlds, described as the ISPOR/ICER meme or belief system for inventing (non-evaluable by design) value claims for cost-effectiveness, and in a more recent paper in F1000Research detailing the options for bias in lifetime models and the opportunities to use the model framework (the ICER reference case) as a marketing device to support a sponsor's product with ersatz cost-effectiveness claims ⁶⁷⁸⁹. Your effort to assess effectiveness and value for oral and monoclonal antibody treatments for multiple sclerosis is, once again, by the standards of normal science and Rasch measurement, an analytical dead-end.

In order for you and your academic consultants to actually come to terms with Rasch measurement, which you will deny by retreating to your strange claim that health economists have confidence

that EQ-5D-3L/5L utilities are ratio measures in disguise might I, to emphasize the importance of the Rasch model, quote in full (as I did in my previous letter) the abstract from a 1989 commentary by Wright and Linacre:

Quantitative observations are based on counting observed events or levels of performance. Meaningful measurement is based on the arithmetical properties of interval scales. The Rasch measurement model provides the necessary and sufficient means to transform ordinal counts into linear measures. Imperfect unidimensionality and other threats to linear measurement can be assessed by means of fit statistics. The Rasch model is being successfully applied to rating scales¹⁰.

To which we might add that interval scales are only relevant if we are measuring a single attribute; confounding different attributes into a single score is hazardous and unacceptable. If an entity of interest has a number of attributes of interest, then they must be assessed individually. Questionnaire items must, therefore, relate to a single underlying attribute; otherwise, our scores and claims for response to therapy are unintelligible.

While the standards for Rasch analysis or modern measurement theory have been in place for some 50 years, I appreciate that you and your academic consultants have not been introduced to these concepts and measures which are becoming more widely used in health technology assessment. It is, of course, a lot easier to simply believe, or have confidence, that multiattribute preferences are ratio scales. After all, with the relativist position held by many in health technology assessment it must be true because leaders claim it is true; consensus reigns. In any event, I don't want to go over the arguments presented in my letter of 1 November last for fezolinetant. You have not replied as yet (early days) but I presume you will offer your stock response that because all have confidence in a ratio scale, it must be true. If, however, you and your consultants wish to pursue modern measurement standards in more detail may I recommend chapters 1 - 3, 13 of Bond *et al* ³ and chapters 1 and 2 of Andrich and Marais⁴. In addition, I am currently presenting a graduate level course in the School of Pharmacy, University of Wyoming (Principles of Health Economics and Outcomes) which is focused on a new start in health technology assessment emphasizing the need to recognize the standards of normal science and response defined in terms of modern measurement theory; abandoning lifetime assumption driven simulations that produce imaginary cost-effectiveness claims. The course will be offered again in Spring 2023; I encourage you to consider it for your staff and consultants as credits (3) are awarded which can be applied at other universities.

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 ^{11 12}. Not surprisingly, PRIMUS was overlooked by ICER in the 2017 evidence report ^{13 14}.

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 gage 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.

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 World Health Organization (WHO) classifications for impairment (physiological and anatomical) and activity limitations (capacity and 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.

The PRIMUS-QoL scale comprises 22 binary response items (True/Not True); examples include:

- I'm neglecting my appearance
- I feel as if I have nothing to offer anyone
- I avoid physical intimacy
- My self-confidence is affected
- I don't like staying away from home

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 ¹⁵, 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 ¹⁶. 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 ¹⁷.

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 18 .

Yours sincerely

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I probably have a different type of MS than what majority of other patients have. I don't know what it is but I do know that I've had numerous MRIs—I've had MS for 33 years—and nothing ever shows up on the white matter of the brain. However, a few years ago I took part in a study that included T7 MRIs looking at grey matter. Those MRIs showed lesions. But for the general population, we're primarily looking at white matter, not grey matter.

When I was still able to work, I spoke with a clinician in my office who believed the MS was attacking my autonomous nervous system, but my doctor didn't believe me. But now we know that that happens, and that's what's caused my relapses. And my relapses are always different but my vitals skyrocket each time. I had a stroke this past June and I believe that my MS caused a surge in vitals that then caused the stroke. The cardiologist I saw told me it could be a stroke or it could be MS – he didn't know.

I believe we aren't focused on researching the proper treatments. Many DMTs have been approved but they all operate similarly and none delay progression. There's no evidence that these drugs work in the long-term. Would I deny anyone medication? Of course not, but I think we need to be looking elsewhere.

When I was on Tysabri for two years, I met a patient who hadn't had a relapse in seven years thanks to the drug. But Tysabri didn't work for me because I had relapses every six months. My MS actually got worse on Tysabri. I stopped it and a pharmacist put me on a low-gluten diet and suggested hormone therapy, which I think plays a role in MS. Not enough research has been conducted on hormonal involvement. When a woman with MS is pregnant, she doesn't have relapses, but after the baby is born, she's much more likely to have a relapse. I had my biggest relapse in August 2012 when I was 44, just starting menopause. Is that a coincidence?

During that relapse in August 2012, my vision had been affected for the first time ever. Instead of double vision, I had quadruple vision. I also had the same numbness I've had since day one, which is what led to my initial diagnosis. But all of my relapses are slightly different so doctors will tell me I'm not really relapsing but I know a relapse... it's my body.

I'm not currently on any medication, and I went two and a half years without a relapse. Before I stopped all medication, I also tried Ocrevus when it came out as I liked the idea that it targeted B cells, not T cells. On Ocrevus, I went nine months without a relapse but then had two relapses that each lasted four months. I also feared PML, and worried about the risk despite having low JVC levels – I didn't want to be the one in 1,000 to get PML. But I still gave it a two-year trial. For the first year, I was sick eight out of 12 months. What are the long-term effects of that kind of inflammation?

I've had to make accommodations in my life following relapses. It really became a problem when my symptoms progressed past numbness. Interestingly, my symptoms worsened after I tried Avonex in 1997, and has gotten progressively worse since I've used other DMTs. Is that normal disease progression or did DMTs worsen my MS? During my latest relapse, I started experiencing worse physical symptoms like limping. I wasn't able to drive for two years. I find canes are more of a hindrance. My walker is helpful as are my wheelchairs and scooters I use to walk my dogs. I've implemented changes to my diet as well.

I've done a lot of research on MS for the last 10 years and I've become increasingly interested in stem cells, particularly autologous stem cells. But because my MRIs never found lesions on my white matter, I

wasn't approved for stem cells. Fortunately, I've since learned of a different kind of stem cell and I'm waiting on a screening early next year to see if I'm eligible. We should be pursuing more research in this area instead of DMTs, which I don't believe improve disability in the long run. I've also conducted research on parasitology as doctors have found in autopsy that MS patients have parasites in their brains that affect the nervous system. It's unclear to me why more research isn't being conducted in this area. Based on this research, I saw a naturopathic doctor who conducted a workup and found bacterial biofilms behind which parasites were hiding.

We aren't doing enough to find the root cause of MS. Without this knowledge, how do we treat it? The NIH is conducting a longitudinal study that will be helpful, but we also need short-term studies to understand MS occurrence. And we should be expanding trials outside of DMTs. Years ago, I was denied plasmapheresis – who knows if that could've kept me in the workforce.

We need effective treatments to turn back the clock. I can't walk, I haven't driven since before my stroke this year. I'm unable to write anymore – I haven't written in years. I get terrible tremors and I can barely feed myself. A treatment that restored my hand dexterity would be huge. I do physical therapy for my MS but current treatments don't help me.

Many people with MS don't fall into the 80-20 rule, and there are thousands of patients like me that doctors don't know how to help because DMTs don't work. Part of the problem is that many doctors don't believe us. If we feel like something in our bodies is wrong, we should be trusted because we know our symptoms better than anyone.

-- Lisa Carr