Biogen welcomes the opportunity to comment on the Institute for Clinical and Economic Review's (ICER) *2022 Assessment of Treatments for Multiple Sclerosis*. Multiple sclerosis (MS) is a complex, heterogeneous and chronic disease which has a significant impact on people living with MS and their caregivers.[1,2] With a mean age of diagnosis around 30 years[3], MS disproportionately affects individuals during the main working and reproductive years of their lives.[4] A patient-centric approach is critical when assessing disease modifying treatments (DMTs) for people living with MS. On average, affected individuals are expected to live with MS for over 40 years,[5] it is therefore essential that we have in mind the entire treatment journey whereby treatment choice changes and varies with disease characteristics. Biogen believes the ideal way to support people living with MS is to have the right treatment, at the right time in the disease course, for the right patient. Especially for this complex disease, shared decision making between health care professionals (HCPs) and patients is paramount to improve long term outcomes and quality of life.

As pioneers in neuroscience, Biogen discovers, develops, and delivers worldwide innovative therapies for people living with serious neurological diseases as well as related therapeutic adjacencies. Biogen has dedicated extensive efforts to understand neurology and more specifically MS for more than four decades and to research and develop multiple treatment options that have improved the lives of people living with MS. Biogen supports the MS community in a variety of ways, including patient support services, educational programs, as well as caregiver forums. Given the heterogeneity of MS, a complex autoimmune disease, Biogen is driven by a patient-centric approach, advocates for individual treatment choice and applauds the expanding number of DMTs that have been approved for MS. Biogen is pleased that ICER recognizes the patient burden, the need for comprehensive care and the shared decision making approach to treatment in MS, especially in the background sections of its draft scoping document, which is also reflected in the stakeholder input collected for this large class review.

We appreciate ICER's continued efforts to incorporate factors important to both people living with MS and their caregivers, and we believe the draft background and scope captures many important elements for a review of DMTs in MS. We would like to highlight a few important considerations:

1. **Biogen strongly believes that the included interventions should have an approved indication for treatment in MS, granted by the Food & Drug Administration (FDA). Accordingly, Biogen recommends that rituximab and its biosimilars should be excluded from this review.**

Rituximab is not approved by the FDA or any other regulatory agency for use in people living with MS. While we acknowledge that there are some trials of rituximab in MS, that evidence is still limited,[6] and combined with the lack of RCT trials that have been assessed for regulatory approval, the inclusion of rituximab and its biosimilars in the framework is unlikely to lend itself to rigorous indirect comparisons and will likely introduce bias into the overall decision framework.

2. **The population defined as "relapsing forms of MS" is significantly heterogeneous in different stages of inflammatory disease progression and, in line with the 2017 ICER MS assessment,[7] analyses should be conducted separately for the relapsing remitting MS (RRMS), secondary progressive MS (SPMS) and clinically isolated syndrome (CIS) patient populations.**

Biogen acknowledges the recent FDA decision to update and broaden the definition for RRMS in the product information of all MS DMTs using the "relapsing forms of MS" definition. However, from a clinical and evidence perspective, RRMS, active SPMS and CIS are very different study populations. For example, CIS patients tend to be younger, with lower disability while active SPMS patients tend to be older, have relative severe disability (Expanded Disability Status Scale (EDSS) above 4) and are predominantly in the neurodegeneration phase of MS.[8,9,10] In summary, each of these phases is associated with significantly different underlying disease pathophysiology likely leading to different

treatment effectiveness. As such, Biogen recommends that ICER analyzes these sub-populations separately, with a base case on RRMS.

3. **Detailed inclusion and exclusion criteria to assess which clinical trials will be utilized for the comparative analysis should be reported, and a feasibility assessment should be performed to inform which studies are sufficiently comparable for inclusion in the indirect comparison. Biogen also recommends justifying the choice of all comparators and pre-specifying the interventions and comparators of interest for the comparative value analysis.**

Indirect methods are generally considered acceptable if applied with consideration of the basic assumptions of homogeneity, similarity, and consistency.[11] The patient population included in current trials tends to be different compared to the earliest trials in RRMS (conducted in 1990s), with regards to MS natural history, mean age, current treatment options, MS diagnosis criteria, previous immune suppressant treatment history, etc.[12] There have also been variations in inclusion criteria of the trial populations and endpoint definition across clinical trials (variations in definition of relapses, no evidence of disease activity, etc.) and multiple evolutions in technology (e.g. MRI) to detect certain outcomes.[12] Therefore, the inclusion of different studies may introduce chronological bias and thus confound the analysis. This can be mitigated by limiting comparison of outcomes across interventions that have conducted more similar and homogenous trials (e.g. within anti-CD20 class, S1P class, etc.). To that effect Biogen recommends pre-specifying the intervention and comparators of interest for the comparative value analysis in the final scope, which should also be combined with a consistent and objective justification for choosing interventions and specific comparators for the comparative value analysis.

4. **Methodologically, evidence from randomized controlled trials (RCT) should not be combined with non-randomized comparative cohort studies.**

As noted above, indirect comparison of clinical data requires careful consideration of homogeneity, similarity, and consistency.[11] The inclusion of comparative cohort studies in such analysis would break such assumptions and therefore we advise against the combination of randomized and non-randomized evidence. Furthermore, we believe it is important for ICER to pre-specify in the research protocol how it plans to assess the quality of the evidence to be included in the analysis.

5. **Biogen would welcome more clarity on the specific scales ICER is intending to use to measure the broad set of outcomes listed in the draft scope. Given the chronic nature of these treatments, Biogen recommends that ICER appropriately captures treatment tolerance in its assessment as a key factor that characterizes available DMTs.**

Biogen welcomes the large set of outcomes listed, since they allow the collection and valuation of a broader set of patient dimensions that are important to the quality of life for people living with MS. Biogen recommends pre-specifying which scales ICER intends to use to measure each outcome listed in the draft scope document.

MS Treatment should be customized according to a multifaceted benefit-risk assessment.[13] Tolerance is an important component of that assessment. The American Academy of Neurology's treatment guidelines state that "*Clinicians must ascertain and incorporate/review preferences in terms of safety, route of administration, lifestyle, cost, efficacy, common adverse effects, and tolerability in the choice of DMT in people with MS being considered for DMT*."[14] Biogen recommends adding "tolerance to side effects" to the proposed list of patient-important outcomes. Significant innovation in MS has resulted in new treatment options that address specific tolerance issues seen with older treatments, such as reducing cardiac effects or minimizing gastrointestinal issues, among others.

6. **Given the significant impact to people living with MS and their caregivers, Biogen recommends prioritizing the societal perspective in the base case of the comparative analysis.**

The value of medical interventions is multifaceted and should be assessed from a broad societal perspective which also captures the impact of the disease on caregivers and families. The burden on caregivers and families of people living with MS is significant.[15,16,17] Caregivers carry significant indirect costs and suffer from absenteeism and presenteeism which add considerably to the societal costs of the disease.[18] Therefore, Biogen recommends including in the base case cost-effectiveness analysis the societal perspective that includes indirect costs and health and economic impact on caregivers, as the most suitable for policy decision-making.

7. **Natalizumab Extended Interval Dosing (EID) is associated with lower probability of Progressive Multifocal Leukoencephalopathy (PML), while providing a high level of efficacy in controlling MS disease activity and reducing real-world costs of treatment.**

Real-world use of MS medications could be different from the use in the clinical trial setting. As observed in clinical practice, the natalizumab dosing interval is lengthened (average of six-week dosing, EID), often to mitigate safety concerns, while the approved dose is every four weeks.[19] A retrospective safety analysis of the TOUCH Prescribing Program showed that an EID (average six-week dosing) schedule is associated with an 88 percent reduction in the probability of developing PML.[20] PML is an important side effect associated with natalizumab and other MS DMTs. Given the improved safety profile of EID with natalizumab, Biogen conducted the Phase IIIb NOVA Study (NCT03689972), a randomized, controlled clinical trial.[21] The study found that efficacy was maintained in patients who switched after one year from every four-week dosing to every six-week dosing.[21] This lower frequency of use leads to a reduced annual cost of therapy for some patients, which should be accounted for in the comparative value analysis. Biogen therefore recommends that evidence on real-world use of natalizumab, including a reduction in probability of PML and a reduction in annualized treatment costs of natalizumab, is accounted for during this evidence review.[22]

In summary, Biogen believes in the importance of allowing people living with MS access to the full range of treatment options available on the market, considering the heterogeneous needs of the MS population. Shared decision making varies for each person living with MS taking into account their MS severity at diagnosis and/or what stage of the disease they are in.[13]

Over the past four decades, Biogen has been committed to translating science to meaningful advances for the MS community. Our industry-leading portfolio and continued investment in our products enables us to offer a broad range of options to meet the ever-evolving needs of the MS community and drive greater individualized disease management. We caution that a cost-effectiveness analysis may have limits in capturing the complexities and nuance of MS disease management for the individual patient. If applied incorrectly, conclusions drawn from a simplified analysis in this complex disease could adversely impact people living with MS. Biogen supports patients' ability to choose, with their HCP, the most appropriate medication individualized for them. We welcome further conversation with respect to input into this analysis.

Sincerely,

Carlos M. L. Acosta

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

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Bristol Myers Squibb™

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Submitted via email: publiccomments@icer.org

May 12, 2022

RE: Draft Scoping Document titled "Treatments for Multiple Sclerosis: Effectiveness and Value"

Dear ICER Review Team,

Bristol Myers Squibb (BMS) acknowledges the importance of fully and accurately understanding the value that innovative therapies provide to patients, and we appreciate the opportunity to comment on the Institute for Clinical and Economic Review's (ICER) draft scoping document titled "Treatments for Multiple Sclerosis: Effectiveness and Value". At BMS, our mission is aimed towards discovery, development and delivery of innovative medicines that help patients prevail over serious diseases.

We ask that ICER consider the following comments and recommendations at this early stage in the assessment process.

1. **BMS recommends adjusting for reference arm response in the network meta-analysis (NMA) of disease modifying therapies (DMTs) for the treatment of multiple sclerosis (MS) to assess and reduce the risk of bias**.
   Reference arm outcomes are highly heterogenous across trials in MS. For example, annualized relapse rate (ARR) varied from 0.34 [1] to 1.38 [2] and 24-week confirmed disability progression (CDP) varied from 10.2% [1] to 35% [3] across placebo arms in the trials included in the corresponding NMA in ICER's 2017 review of DMTs for MS.[4] Such heterogeneity can confound traditional anchor-based NMA analyses; NICE DSU has issued recommendations on how to appropriately adjust for reference arm response to address this issue.[5-9] Indeed, such methods were adopted by ICER in their 2018 review of treatments for psoriasis.[10] If such adjustments are not technically feasible given data limitations (e.g., too few trials to reliably estimate the placebo-arm effect) then the inability to adjust for what is a crucial confounding factor — i.e., the outcome

level on the placebo arm which varies considerably across trials — should be noted as an important limitation of the NMA.

2. **BMS recommends that ICER include only those therapies approved or under review by the FDA for the treatment of MS in their assessment. Rituximab, in particular, should be excluded from the assessment.**

   At present, rituximab has neither been approved nor is being sought for approval by the FDA for the treatment of MS. Without FDA approval or inclusion in MS treatment guidelines, there are no consensus dosing regimens for rituximab for the treatment of MS.[11] Additionally, in the 2017 review of MS, ICER determined that the clinical evidence on rituximab was inconclusive, and there was no clinical evidence for rituximab's impact on CDP in this population. To our knowledge, no new evidence from randomized clinical trials has accrued to support review of rituximab for the treatment of clinically isolated syndrome (CIS), relapsing-remitting MS (RRMS), or secondary progressive MS **(**SPMS).[4]

3. **BMS appreciates ICER's recognition of the limitations of the Expanded Disability Status Scale (EDSS) for measuring progression and economic value in MS. We recommend additional evidence and citations on this topic for ICER's consideration.**

   Disability due to MS is typically assessed using the EDSS. However, as ICER notes in their draft scoping document, there are important limitations associated with EDSS as a measure of disability and disease progression in MS. The following evidence is important for decision makers to keep in mind when interpreting MS clinical trials or economic analyses based on EDSS outcomes.

   - CDP, defined as serial evidence of clinical worsening based on EDSS, forms the critical link between clinical trial outcomes and economic models, but has limited prognostic value for disability. In a large US-based, long-term study of patients with MS, CDP had limited prognostic value for time to next EDSS progression, time to EDSS 6, and time to SPMS, raising questions about the reliability of lifetime projections of EDSS in any economic model based on 2-year clinical trials that measure progression using CDP.[12]
   - CDP may overestimate the accumulation of irreversible disability as studies have shown that the extent of disability may be sustained or even regress over time in a number of patients. In a retrospective analysis of the global MSBase cohort study, up to 30% of progression events based on 3-6 month confirmed disability had subsequent regression of disability.[13] In an

analysis of placebo arms in two RRMS randomized clinical trials, CDP was maintained over two years in fewer than half of the patients. [14] In a separate analysis of the CLIMB study, nearly half of the patients who experienced disability progression did not sustain it over the duration of follow-up.[15]

- EDSS may both worsen and improve significantly over time, which is inconsistent with economic models that assume EDSS can only worsen. For example, in an analysis of placebo arms in 31 randomized clinical trials, the rate of EDSS improvement could be substantial, and at times was equivalent to the rate of EDSS worsening in both RRMS and SPMS patients.[16]

4. **BMS appreciates ICER's inclusion of preservation of brain volume and reduction of lesions in their evaluation of treatments for MS and supports the inclusion of patient relevant endpoints such as cognition and fatigue.**

   Multiple systematic reviews of clinical trials in MS,[17,18] and longitudinal cohort studies,[19,20] have positively associated T2 lesion and brain volume with disability accumulation. In addition, both brain volume loss and significant numbers of new T2 or gadolinium enhancing lesions are predictive of subsequent disability progression [19-21] — indeed more predictive than short-term changes in EDSS.[15] Incorporation of MRI outcomes is essential for any comprehensive evaluation of MS treatments. In addition, we appreciate ICER's inclusion of endpoints such as cognition and fatigue which are important markers of disease progression and quality of life in MS.[22-25]

Thank you for the opportunity to review and comment on this draft scoping document.

Sincerely,

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Genentech
A Member of the Roche Group

May 12, 2022

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

Dear ICER Review Panel:

Genentech, a member of the Roche group, appreciates the opportunity to provide input on *Treatments for Multiple Sclerosis: Effectiveness and Value: Draft Background and Scope* [1]. Ocrevus® (ocrelizumab) is the first and only FDA-approved disease-modifying therapy (DMT) that is indicated for the treatment of adults with either relapsing forms of multiple sclerosis (RMS) or primary progressive multiple sclerosis (PPMS) [2]. We are confident in the value that ocrelizumab continues to bring to patients since its approval in 2017.

Leveraging our experience with the previous ICER reviews in multiple sclerosis (MS), we have four key recommendations for this assessment:

1. Rituximab should be excluded from this review as it is not FDA-approved for the treatment of MS, and external bodies have consistently concluded there is insufficient evidence to support its use in MS.

2. Given the early age at diagnosis and the progressive nature of RMS, long-term outcomes, including confirmed disability progression (CDP) and confirmed disability improvement (CDI), should be a key focus of ICER's review.

3. Due to changing diagnostic criteria and increasing selection bias in clinical trial populations, ICER should carefully evaluate and elucidate differences in the clinical characteristics of trial participants, and leverage published natural history data in lieu of data from placebo arms of recent trials.

4. ICER should consider and clearly delineate the limited clinical evidence required for abbreviated approval of bioequivalent and biosimilar drugs using the 505(b)(2) and 351(k) regulatory pathways.

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

1. Rituximab should be excluded from this review as it is not FDA-approved for the treatment of MS, and external bodies have consistently concluded there is insufficient evidence to support its use in MS.

***Rationale*:** Inclusion of rituximab in the review of treatments for RMS would be inappropriate given the lack of FDA approval or robust scientific data in this disease area. Rituximab was studied in a small Phase II trial of subjects with RMS (n=104), which only assessed a single course of rituximab and had a limited follow-up period of 42 weeks [3]. This trial did not lead to an FDA-labeled indication in RMS. In addition to the lack of sufficient data to demonstrate benefit, it is imperative to note rituximab's multiple boxed warnings may result in an unbalanced benefit-risk assessment, thus making it an unsuitable choice for treatment of MS [4].

Further supporting the exclusion of rituximab, multiple external bodies have consistently concluded that there is insufficient evidence to support the use of rituximab in RMS. We highlight these perspectives below:

- A 2018 AAN systematic review of DMTs found the evidence to support rituximab's efficacy for reducing the annualized relapse rate (ARR) was "insufficient to support or refute" [5], and thus, it is not included as a recommended therapy in the AAN practice guidelines [6].
- A Cochrane network meta-analysis comparing rituximab to other DMTs found insufficient evidence to support the use of rituximab in relapsing-remitting MS (RRMS) [7].

- In the 2017 review of RRMS therapies, ICER concluded the evidence on rituximab was "promising but inconclusive" [8]. The clinical evidence base for rituximab in MS is largely unchanged since the previous review; therefore, it would be difficult to justify a different conclusion in the current review.

Genentech market research data also suggest the use of rituximab, including Rituxan® and biosimilars, represents ≤5% of total patient market share in RRMS [9]. *Commercial-in-confidence* data submitted.

Per the current ICER value assessment framework, "relevant comparators are selected through a survey of clinical guidelines from professional societies, consultation with clinical experts and patients, and review of clinical trial designs" [10]. Moreover, best practices for economic modeling recommend that the ideal comparator should be widely used in practice [11]. Given these documented guidelines, the rationale for the inclusion of rituximab is not transparent or evidence-based at present.

***Implications*:** The inclusion of rituximab would imply its body of evidence is consistent with other FDA-approved therapies. This may be misleading for reviewers of ICER's report who lack the context above.

2. Given the early age at diagnosis and progressive nature of RMS, long-term outcomes, including CDP and CDI, should be a key focus of ICER's review.

Rationale: The onset of RMS typically occurs during an individual's peak productive years (~30 years of age); therefore, the disability associated with MS impacts daily functioning, work productivity, and quality of life for decades to come [12,13]. Prevention of disability is thus an essential goal in the treatment of MS. While ARR is frequently leveraged as a measure of inflammatory activity, it fails to account for the variability in severity, duration, resource utilization, and resultant disability associated with relapses [14]. People with MS may still experience irreversible disability despite treatment with a DMT [15] and prefer treatments which prevent long-term progression rather than relapses alone [16].

In contrast, measures of progression reflect accumulation of clinical disability from inflammatory or neurodegenerative disease processes, resulting in a better assessment of long-term disease worsening that may occur independent of relapses [17]. The importance of progression as an endpoint is further underscored by a recent analysis which found that most disability accumulation in RMS is <u>not</u> associated with relapses [18].

Furthermore, early intervention to delay progression may help reduce the longer-term direct and indirect cost burden [19,20]. Research has found that MS-related costs increase rapidly over time as patients progress, primarily driven by the increased need for informal care, mobility aids, transportation, and home modifications, combined with substantial reductions in work productivity and employment [12,21-23].

Finally, the emergence of high-efficacy DMTs has raised awareness of the importance of CDI as a long-term outcome. For those therapies with a demonstrated impact on CDP, CDI elucidates whether these treatments may not only help slow progression, but may demonstrate ability to restore function over time [24]. CDI is increasingly used as a measure in clinical trials and is an important consideration in the selection of treatment.

Implications: Selection of the appropriate outcomes is imperative to ensure a holistic evaluation of the true impact of disease and the benefit of treatments. A focus on short-term outcomes, such as ARR, would underestimate the full impact of MS on patients and the health care system more broadly.

3. Due to changing diagnostic criteria and increasing selection bias in clinical trial populations, ICER should carefully evaluate and elucidate differences in the clinical characteristics of trial participants and leverage published natural history data [25,26] in lieu of data from placebo arms of recent trials.

Rationale: As noted by ICER in the 2017 review [8], the diagnostic criteria for RMS have changed numerous times since the approval of the first DMT [27-29]. These changes have allowed much earlier diagnosis of

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RMS, especially for those who would have been previously classified as having clinically isolated syndrome (CIS), thereby effecting a stage migration that has fundamentally changed the natural history of RMS [30,31].

Further, the availability of new treatment options has led to a shift in clinical trial populations [32]. Individuals with more aggressive MS are often not considered for placebo-controlled trials as the risk of randomization to placebo could result in harm in the form of irreversible disability progression, thereby resulting in a selection bias for individuals with less severe MS.

Finally, the definition of a relapse has become more stringent since the initial trials of injectable DMTs were conducted; indeed, more recent Phase III trials in RMS have required relapse adjudication with a demonstrable increase in the Expanded Disability Status Scale [14,32,33].

Implications: Natural history studies or placebo arms of the earliest trials will provide a more truthful representation of the natural history of MS, allowing for more accurate and consistent assessment of the benefits of DMTs. Failure to do so may result in false or misleading conclusions.

4. ICER should consider and clearly delineate the limited clinical evidence required for abbreviated approval of bioequivalent and biosimilar drugs using the 505(b)(2) and 351(k) regulatory pathways.

Rationale: The proposed scope of ICER's review includes a number therapies that were approved by the FDA through non-traditional pathways or are not FDA-approved. We summarize below:

- Rituximab biosimilars, diroximel fumarate, and monomethyl fumarate were approved on the basis of pharmacokinetic (PK)/pharmacodynamic (PD) data and have insufficient efficacy/safety data in RMS.
- Bioequivalent teriflunomide was leveraged as a comparator in the ULTIMATE I and II studies [34,35], but remains an unapproved treatment for which no publicly available data on PK/PD or efficacy/safety exist; thus, there are challenges in the ability to assume bioequivalence to Aubagio®.

As ICER seeks to draw conclusions on the comparative clinical value of available treatments through formal evidence synthesis and deliberation during the public meeting, this information should be made transparent to allow for correct interpretation of risks, uncertainties, and conclusions on comparative value.

Implications: The review will require making comparisons of treatments that are highly variable in terms of regulatory approval status and pathways. In the absence of published best practices or formal ICER guidance on how to best synthesize and interpret this heterogeneous evidence, external stakeholders will be reliant on ICER's expertise to understand the uncertainties and caveats. If ICER is not transparent in discussing these data limitations, the results of the clinical effectiveness review may be misinterpreted by end users.

In closing, we thank you for the opportunity to provide feedback and look forward to continued dialogue and engagement with ICER. Genentech is committed to delivering innovative and transformative treatments for people with MS, and we continue to grow our expertise in this space. We provide these recommendations with the intent to support a rigorous assessment that appropriately accounts for the strengths and limitations of evidence, ensures patients' access to the therapies they need, and represents the interests of all stakeholders.

Sincerely,

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May 12, 2022

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Re: Draft Scoping Document for ICER Review: Multiple Sclerosis: CIS, RRMS, and SPMS- An assessment of treatments for multiple sclerosis

On behalf of the Multiple Sclerosis Coalition (MSC), a 501 (c) 3 network of nine MS organizations, thank you for the opportunity to comment on ICER's Draft Scoping Document for *An assessment of treatment for multiple sclerosis.* Given the number of multiple sclerosis (MS) disease modifying treatments (DMTs) on market, we understand ICER's desire to update the MS review. 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. Thus, it is important that an assessment of treatments for MS considers real world implications of recommendations rather than approaching the assessment from an academic standpoint.

Population

Highly heterogeneous disease

As ICER notes in the draft scope, MS is a chronic, autoimmune disorder of the central nervous system. Symptoms vary by individual and range from numbness or tingling, to walking difficulties, fatigue, pain, depression, cognitive challenges, vision and more. Due to significant disease heterogeneity, current clinical practice guidelines recommend considering the risks and benefits of each treatment strategy on a patient-by-patient basis.[1] DMTs are important in disease modification but must be combined with symptom management and mental health services to provide comprehensive care.

> The presence of comorbidities, including depression, anxiety, and vascular risk factors, are associated with a diagnostic delay between symptom onset and diagnosis, disability progression, and health-related quality of life.[2]
>
> Current guidelines recommend clinicians consider patient preferences related to safety, route of administration, lifestyle, cost, efficacy, common adverse effects (AEs), and tolerability when deciding among DMTs.[1] Careful, individualized consideration of treatments is needed because initiation of one DMT can impact the safety and efficacy of subsequent DMTs.[3]

The scope references a study that DMT discontinuation may be considered in older, stable people with MS. There are still limitations in knowledge regarding DMT discontinuation.[4] Three ongoing randomized clinical trials will provide significant data regarding outcomes of discontinuation and it may be premature to consider such a recommendation at this time.

Stakeholder Input

Representativeness & overcoming disparities

The members of the MS Coalition are committed to research that is representative of diverse patient populations. We appreciate ICER's recognition that subgroup analyses, including by

race/ethnicity are important. This need is evidenced in a recent analysis which demonstrated a greater burden of disease among black people with MS as compared to white people with MS, even after adjusting for socioeconomic indicators.[5] However, we are concerned that lack of data, especially when relying on clinical trials alone, will impede this subgroup analysis, resulting in conclusions that are not generalizable. Additional data beyond clinical trials is needed for a more complete understanding of racial, ethnic and other differences.

Furthermore, data collection tools, such as the patient questionnaire are only available in English. To reduce data gaps in the future, we recommend that ICER translates the questionnaire into Spanish to facilitate the collection of more representative data.

General Neurologists

Several studies document that prescribing habits of general neurologists differ from prescribing of MS specialists.[6] General neurologists prescribe a higher portion of older DMTs and DMTs that may be perceived to have more safety data or ease of initiation.[7] Many people with MS receive care from these neurologists and this group's input may be missing from the stakeholder input collected..

Comparators and Interventions

With more than 20 DMTs across different mechanisms of action and routes of administration, we understand ICER's desire to narrow the number of comparators reviewed in the report.

MSC does urge ICER to carefully consider how findings from the planned evidence report will add to knowledge about MS treatment and care and real-world implications to patients' access to care.

The interventions/comparators analyzed across the studies described in the draft scoping document vary considerably, potentially leading to confusion or incorrect assumptions on the part of readers. For example, the proposed clinical evidence review includes monoclonal antibodies and oral therapies (fumarates, S1p receptor modulators, and teriflunomide). Whereas the proposed cost-effectiveness model includes at least ofatumumab and ublituximab as compared to dimethyl fumarate and fingolimod, while the proposed budget impact analysis is limited to ublituximab. If these types of differences remain across the different analyses, we encourage ICER to be clear about how and why these decisions were made.

Outcomes

We appreciate ICER providing a comprehensive list of outcomes in the scoping document. DMTs are intended to reduce MS relapses and MRI activity, however, they are not prescribed to address symptoms of MS, including several of the outcomes listed in the draft scoping document. PwMS receive additional treatments to address symptoms.[1,8] A comprehensive approach to treating MS is necessary and should be reflected in the analyses, including being appropriately represented in the total cost of care. Outcomes of interest related to the DMTs and relevant to people with MS that should be addressed include adverse events, risks, impact on vaccine response and family planning. Sites of care are important considerations: patients may be seen in clinics by residents or fellows resulting in non-continuous care and altered communication patterns.

Scope of Comparative Value Analyses

Model structure must accurately reflect patients' experiences living with and treating MS

When developing the model structure, we encourage ICER to review not only the past models referenced but also recent publications evaluating those models and offering recommendations for future economic evaluations in MS.[9–13] For example, many of the recommendations described by Hernandez and colleagues are aimed at developing models that better reflect patients' experiences living with and treating MS, including modeling disease progression, treatment sequencing, treatment discontinuation, and other health outcomes (e.g., relapses avoided).[9]

Health care sector perspective should appropriately reflect total cost of care and modified social perspective analyses must also holistically represent

We encourage ICER to review the recently published study "The Economic Burden of Multiple Sclerosis in the United States: Estimate of Direct and Indirect Costs" when estimating direct, indirect, and non-medical costs to inform the healthcare and societal perspectives.[14] The study provides estimates from 2019 of direct costs, including hospital inpatient stays, physician office visits, prescription medications, administration of prescription medication in the outpatient setting, durable medical equipment, outpatient services, and nonacute institutional care. The study also provides estimates of indirect (e.g., productivity loss for those in the labor force) and nonmedical costs of MS (e.g., formal daily care, modification to homes, purchases of special motor vehicles). Survey data used to estimate nonmedical costs can be made available to ICER researchers upon request.

From a patient perspective, total cost of care for a DMT may include required monitoring or testing for either initiation or ongoing monitoring, and treatment administration/infusion costs. Indirect and non-medical costs are considerations as well, including things like travel to receive treatment and missed work hours for the person with MS or care partner.

MS progression, and especially acute relapses, have a significant emotional impact on patients and caregivers.[15–17]

There can be devastating emotional, financial and health consequences for people with MS who are on a DMT that doesn't work for them or can't access a DMT that their provider recommends.

Identification of Low-Value Services

We applaud ICER's focus on reducing wasteful services. However, given patient heterogeneity, the variety of treatments to address symptoms, and existing challenges related to utilization management, we urge ICER to use caution when designating services as wasteful or lower-value.

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

Respectfully submitted on behalf of the MS Coalition,

Bari Talente
MS Coalition President

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Appendix

MS Coalition Organizations

Accelerated Cure Project
Consortium of MS Centers
Can Do MS
International Organization of MS Nurses
MS Views and News
Multiple Sclerosis Association of America
Multiple Sclerosis Foundation
National MS Society
United Spinal Association

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Executive Summary

Novartis Pharmaceuticals Corporation (Novartis) appreciates the opportunity to provide feedback on the Institute of Clinical and Economic Review's (ICER) draft scoping document for the assessment of treatments for Multiple Sclerosis. In summary, Novartis respectively offers the following suggestions for consideration:

- ICER should acknowledge evidence that has shown improved patient outcomes with early high-effective therapy use.
- Patient perspective should be included when assessing clinical value.
- Treatments not approved by FDA for multiple sclerosis should not be included in this assessment.
- Consider including immunoglobulin levels for anti-CD20 monoclonal antibodies as an outcome of interest when assessing clinical value.
- ICER should use a weighted average to calculate dimethyl fumarate drug costs.
- ICER should consider costs by site of care for infusible product(s) in the comparative value analyses
- Novartis is open to considering supporting sub-group analyses.

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

Suggest ICER acknowledge evidence that has shown improved outcomes with early high-effective therapy use

In the background section, it is mentioned that "Choice of initial therapy is debatable, with some clinicians and PwMS opting to begin treatment with medications that have moderate efficacy but a better safety profile such as the injectable or oral drugs and escalating as needed; other clinicians and PwMS opt to treat with monoclonal antibodies at diagnosis, which have higher efficacy but a higher risk of serious adverse events." We agree that there many factors to consider when selecting a treatment, however, we suggest that ICER also summarizes evidence has shown improved patient outcomes with early high-effective therapy use.[1] For example, a cohort study of people living with MS showed that those who received high-efficacy treatment had a smaller increase in Expanded Disability Status Scale score at 5 years compared to people who received moderate-efficacy disease-modifying therapy for first-line treatment.[2]

Patient perspectives should be included when assessing clinical value

Patient perspective should be included when assessing clinical value. Shared decision making plays an important role when choosing therapy, as patients and providers must balance considerations around efficacy, safety/tolerability, as well as preference for route, frequency, and length of time of administration. For example, studies have shown that some patients have a strong preference for injectable medications and some for oral medications.[3,4]

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Treatments not approved by FDA for multiple sclerosis should not be included in the final report

We suggest ICER include rituximab and ublituximab only if they receive FDA approval prior to ICER publishing a final report. Inclusion of therapies that have not gone through rigorous FDA review could lead to unintended consequences. For rituximab, we recognize it is currently used off label, however without proper regulatory review on the risk/benefit of the therapy, ICER conclusions may encourage further off label use that could pose unacceptable risks to patient safety.

Immunoglobulin levels over time as a unique AE of interest

B-cell depletion is a function of treatment with anti-CD20 monoclonal antibodies, such as ocrelizumab, ofatumumab, and ublituximab. However, depleting B-cells may lead to decreased immunoglobulin levels (Ig) [6-10] and, consequently, increased risk of infection.[11,12] Immunoglobulin levels over time may be a unique AE of interest to consider including in both the clinical and economic assessments.

Consider a weighted average to calculate dimethyl fumarate drug costs.

With many versions available including generics, to calculate drug cost for dimethyl fumarate, we suggest ICER develop a weighted average based on utilization of the available products to account for the variability in drug costs.

ICER should consider costs by site of care for infusible product(s) in the comparative value analyses

When estimating administration and drug costs of infusible product(s) for the comparative value analysis, ICER should incorporate site of care setting in the assessment. A retrospective cohort study that evaluated real–world cost of care, including direct pharmacy and medical costs over 2 years among MS patients who initiated ocrelizumab, natalizumab, or alemtuzumab showed hospital outpatient department was the most expensive setting for administering the treatments compared to physician office and home setting.[13] Accounting for costs by site of care will more accurately reflect direct medical costs.

Novartis is open to considering supporting subgroup analyses

Data permitting, sub-group analyses could be explored. However, it is important to note that trials may not have been statistically powered for sub-group analysis or randomized on that characteristic. The scientific robustness of the sub-group analysis may be challenging.

We appreciate the opportunity to provide comments for this assessment and feel that consideration should be given to the points we have made to ensure a scientifically sound assessment.

Sincerely,
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May 17, 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 Scoping Document for Multiple Sclerosis

Dear Dr. Pearson:

We appreciate ICER's role in advancing the discussion of value across the US healthcare system and the stated aim of this report to evaluate the health and economic outcomes of treatments for multiple sclerosis (MS). TG Therapeutics is committed to developing novel treatment options for patients with b-cell diseases, including MS, that improve patient outcomes. Given our understanding of the complexities in treating patients with MS, we would like to offer the following recommendations for ICER's Draft Scoping Document (DSD).

ICER should consider including only those interventions and comparators that have or are currently seeking FDA-approved indications in MS

ICER's current DSD includes the assessment of rituximab and rituximab biosimilars. While we recognize that rituximab and recent biosimilar formulations are used in off-label treatment for MS, we request ICER to reconsider including these therapies for the following reasons:

1. Rituximab is not currently indicated for the treatment of MS nor is there an FDA-approved dose for rituximab.
2. The quality of clinical data is expected to be consistent across *approved and investigational* therapies for MS; discrepancies may exist between the design of studies for products that have been or are being used to support FDA approval in MS, which are generally expected be of consistent design and quality, compared to the design of rituximab clinical studies in MS, thereby preventing appropriate comparisons. For instance, the HERMES trial was a phase 2 study of 104 patients with relapsing forms of MS that evaluated the efficacy of rituximab based on MRI scans of the brain, the proportion of patients with relapses, and the annualized relapse rate (ARR); however, the trial did not report disability progression.[1] Moreover, the DELIVER-MS study is a phase 4 randomized controlled trial comparing an early highly effective treatment approach (including but not limited to rituximab) to an escalation treatment approach, which includes initiation with a non-highly effective treatment followed by transition to higher efficacy treatments.[2] However, such a clinical trial design represents a treatment sequence comparison and is thus dissimilar to trial

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designs for regulatory approval in MS. Finally, rituximab is currently being investigated in a prospective, randomized phase 3 study comparing two dosing regimens of rituximab (12-month dosing interval of 500 mg vs. 6-month dosing interval) (RIDOSE-MS); however, the study is a non-inferiority trial and does not include a placebo arm.[3]

3. In addition to the trials cited in ICER's current DSD, ICER references two observational data analyses of rituximab as further rationale for maintaining rituximab within the scope of the current assessment.[4,5] However, the studies did not include a comparison cohort and/or evaluated patient populations outside of the US setting, limiting their applicability to ICER's US health system perspective.

The lack of FDA-approved indications, well-controlled phase 3 studies, and observational data of US-based populations raise concerns for comparing the efficacy and safety of rituximab and its biosimilars to those agents that are approved or seeking approval in MS in the US.

TG Therapeutics requests for ICER to publish its methods for identifying the comparators in the Scope of Comparative Value Analyses

In the section of the DSD titled "Scope of Comparative Value Analyses," ICER indicates that it will compare treatment initiation of selected monoclonal antibodies to "treatment initiation of market leading oral therapies, including at least dimethyl fumarate and fingolimod." Market leaders can be defined using a variety of methodologies and through a variety of data sources. TG Therapeutics requests that (1) ICER is transparent in its process for model comparator selection and (2) industry stakeholders are given the opportunity to provide feedback on its methodology.

TG Therapeutics looks forward to working with ICER throughout this process, and we welcome the opportunity to provide further clarification should ICER have questions on this feedback.

Sincerely,

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