Bayer wanted to ask why Betaseron is being included as one of the comparative agents for secondary progressive MS. Within the US Betaseron is not indicated for secondary progressive MS with minimal clinical data on the use of it in these patients and very limited use of the drug in this area out in the real world. With this background our feeling is that this would not make for an appropriate comparator for the Novartis compound.

While we recognize that drugs are sometimes used off label in the marketplace and can be a somewhat common choice in certain disease categories especially one where there are limited drugs with the indication available to treat these patients, this does not appear to be the case with respect to Betaseron in secondary progressive MS. In addition, there is no gold standard clinical guideline for the treatment of Multiple Sclerosis in the United States. However, DynaMed (which is a clinical repository for recommendations in all disease states using evidence-based methodology) recommends for the progressive component of MS that "the use of either interferon beta or glatiramer acetate is not recommended" in the treatment of these patients.

With this background we would respectfully suggest that ICER consider remove Betaseron from this analysis.

Sincerely,

Todd

Todd Williamson
VP US Medical Affairs, Data Generation & Observational Studies
Bayer U.S. LLC

November 20, 2018

Institute for Clinical and Economic Review
Two Liberty Square, Ninth Floor
Boston, MA 02109

Via electronic mail: publiccomments@icer-review.org

Re: Draft Scoping Document for ICER Review of Siponimod for the Treatment of Secondary Progressive Multiple Sclerosis: Effectiveness and Value

On behalf of the Multiple Sclerosis Coalition (MSC), thank you for the opportunity to comment on ICER's Draft Scoping Document for the Assessment of Siponimod for the Treatment of Secondary Progressive MS. The Coalition was founded in 2005 to improve the quality of life for those affected by MS through a collaborative national network of independent MS organizations. Today, the Coalition has nine member organizations.

Multiple Sclerosis (MS) is a disorder of the central nervous system characterized by inflammation, demyelination and degenerative changes. Symptoms vary by individual and range from numbness or tingling, to walking difficulties, fatigue, dizziness, pain, depression, blindness and paralysis. The most common disease course, relapsing remitting MS (RRMS) is characterized by clearly defined attacks of new or increasing neurologic symptoms, followed by periods of partial or complete recovery. Approximately 85 percent of people with MS are initially diagnosed with RRMS. Secondary Progressive MS (SPMS) follows an initial relapsing-remitting course, and most people who are diagnosed with RRMS will eventually transition to a secondary progressive disease course in which there is a progressive worsening of neurologic function and accumulation of disability over time. SPMS can be further characterized at different points in time as either active (with relapses and/or evidence of new MRI activity) or not active, as well as with progression (evidence of disease worsening on an objective measure of change over time, with or without relapses) or without progression.[i]

Each clinical course of MS presents and progresses differently in every individual. A growing body of evidence indicates that early and ongoing treatment with an FDA approved disease modifying therapy (DMT) is the best way to modify the course of the disease, prevent the accumulation of disability, and protect the brain. There are currently over 14 DMTs available to people with RRMS, and there are multiple variables that go into decision making for the use of these DMTs. While mitoxantrone received FDA approval for chronic progressive MS, a description that is no longer used, it is not commonly used in the treatment of SPMS due to toxicity concerns. This was noted in the draft scoping document. Due to these safety concerns and paucity of use, the Coalition supports ICER's decision to not include mitoxantrone as a comparator treatment.

Background:
We suggest that ICER review the 2014 Lublin, et al. article that defines the clinical course of MS for communication, prognostication, design and recruitment of clinical trials, and treatment decision-making and the 2017 revision of the McDonald criterial for the diagnosis of MS for use in research and clinical practice. As noted in the McDonald revision, at the time of diagnosis, a provisional disease course should be specified (relapsing-remitting, primary progressive, or secondary progressive) and whether the course is active or not, and progressive or not based on the previous year's history. The phenotype should be periodically re-evaluated based on accumulated information. This recommendation is an addition to the 2010 McDonald criteria.[ii]

SPMS cannot be diagnosed outside of clinical observation, and in reality is a retrospective diagnosis characterized by looking back at relapses, disease progression, clinical observations, patient reported outcomes and quality of life issues.

Populations:
Based on the information stated above, the Coalition urges ICER to clarify the target population is all people with SPMS. We urge ICER to avoid using the term "newly diagnosed" to describe the population for comparison in its review. It would be very difficult to ascertain when someone becomes "newly diagnosed" with SPMS. No biomarker currently exists to pinpoint the point of transition; as noted above the transition to SPMS is identified by a retrospective look. Additionally, many physicians are hesitant to diagnose SPMS because of potential impacts on access to treatment. We believe that the appropriate population would be anyone who is eligible to initiate treatment for SPMS.

Scope:
ICER states that evidence will be abstracted from randomized controlled trials (RCTs) as well as high-quality systematic reviews; high-quality comparative cohort studies, and input from patients and patient advocacy organizations, regulatory document data, and manufacturers information. However, as there are no head to head RCTs for SPMS over a sufficient length of time to establish definitive effects on the MS disease course, we urge ICER to address how they will address this significant gap in its review in its final scoping document.

Any clinical and economic review should reflect the current standard of care for people with SPMS. We encourage ICER to consider all available evidence around DMT usage in the current standard of care for SPMS in addition to what is measured in the siponimod trial (if there are differences). We know that current standard of care for SPMS includes the full range of DMTs.

Potential Other Benefits and Contextual Considerations:
While we have had promising conversations to date about patient engagement efforts, we strongly urge ICER to utilize patient engagement to gather evidence and data on other potential benefits and contextual considerations. It is critical that the review reflect the real life experiences, perspectives, hopes and concerns of people living with MS. Many of these aspects inform healthcare decision-making and must be incorporated into the review. The Coalition reiterates our offer to partner with ICER on patient engagement endeavors.

Scope of Comparative Value Analyses:
As ICER considers the inputs into building the model, we encourage you to have in depth conversations with the patients and professional communities about what evidence and studies exist to inform the model.

Additionally, we encourage ICER to consider the price of current disease-modifying therapies in its comparative value analysis. We know that most people diagnosed with RRMS will transition to SPMS. Natural history studies have indicated that 50 percent of those diagnosed with RRMS will transition to SMPS within 10 years, and 90 percent would transition within 25 years. As this transition is more blurred than a clear delineation and many current DMT labels include a broad "relapsing" characterization, many people who might be described as SPMS are currently, or were until very recently, on a DMT. Accounting for this in cost effective and comparative value analyses will be more reflective of what is currently happening in the treatment and care of people with SPMS.

Identification of Low-Value Services:
The final scoping document should include examples of services that ICER views are low-value, as the definition in the draft scoping document is very vague. There must be criteria to determine whether an item is a low value service. We urge caution in using this language because of real world impacts on people with MS.

Other Comments:
The Coalition urges ICER to consider ways to make the comment periods friendlier to patients by offering companion draft reports at an appropriate health literacy level for the general MS population.

Thank you for the opportunity to comment. If you have any questions, please contact Bari Talente, President of the MS Coalition, at bari.talente@nmss.org or 202-408-1500.

Respectfully Submitted on Behalf of the Nine Member Organizations of the MS Coalition
Bari Talente
President

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

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THE CONSORTIUM OF
MULTIPLE SCLEROSIS CENTERS

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Consortium of Multiple Sclerosis Centers: Response to the Draft Scoping Document
Siponimod for the Treatment of Secondary Progressive Multiple Sclerosis
November 20, 2018

The Consortium of MS Centers (CMSC) hereby submits the following comments on the draft scoping document for the review of Siponimod for the treatment of secondary progressive MS (SPMS).

Background:

- A recent study estimated the prevalence of MS in the United States at 947,000 individuals. (Wallin, M. Poster 344. ACTRIMS-ECTRIMS, 2017)
- A 1990's study with interferon beta 1-b showed that SPMS patients with enhancing lesions responded well to the medication while those without enhancement on MRI failed to respond. Therefore, more research needs to be completed in order to better define SPMS.

Stakeholder Input:

- Engagement directly with people living with and/or affected by MS is an essential component of this review. Input from patients must be factored into the analysis and recommendations.

Scope of Clinical Evidence Review:

Analytic Framework: See suggested changes on the attached page

Populations: Due to the difficulty of isolating people living with SPMS, it is important that the scope of the review is limited to those that have initiated (or continued) medication therapy since being diagnosed with SPMS. The population studied should have varied length of time since diagnosis of SPMS, and should not be limited to newly diagnosed SPMS. The question remains: how to diagnose this phenotype.
The decision to focus the review on siponimod appears biased and premature. It is not known whether the FDA will even provide an indication for siponimod use in SPMS. Pricing information is not known and any assumptions about the costs of administration of the drug would be premature.

Comparators:
-Siponimod
-Beta interferons*
-Cladribine*
-Cyclophosphamide*
-Pulse Steroids*
-Glatiramer Acetate*
-Ocrelizumab
-Rituximab
-Natalizumab
-Best supportive care

Comparators must include all DMT's since many patients with SPMS are taking these. To exclude the other medications would create an incomplete analysis.

*additional comparators

The term ‘best supportive care’ must be specifically defined. This was a concern/weakness in the DMT review previously completed by ICER. It must be included in the quantitative review.

Outcomes: (listed in order of importance)
1. Health-related Quality of life
2. Mobility
3. Cognitive function
4. Disability Progression
5. Productivity
6. Caregiver Burden
7. Healthcare Utilization (must include outpatient and homecare services, not just ED and hospitalizations)
8. Relapse
9. Mortality (least important)

The Consortium of Multiple Sclerosis Centers appreciates the opportunity to comment on the draft scoping document. We will be happy to clarify any of the points made herein and will look forward to continued engagement in this project.

Sincerely,

June Halper MSN, APN-C, FAAN, MSCN
Chief Executive Officer

Lisa Taylor Skutnik PT, MA, MA
Chief Operating Officer

enc

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Steven D. Pearson, MD, MSc, FRCP
President
Institute for Clinical and Economic Review
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Boston, MA 02109

November 20, 2018

Re: Siponimod for the treatment of secondary progressive multiple sclerosis – draft background and scope

Dear Dr. Pearson,

Thank you for the opportunity to provide our input regarding the draft scoping document for siponimod in the treatment of secondary progressive multiple sclerosis (SPMS). Below is a summary of our questions, concerns, and recommendations.

1. Comparator selection based on patient population

ICER states that they will evaluate "medications that have shown some efficacy **in progressive MS** and are most used in practice, irrespective of whether they have FDA indications for SPMS." By using the "progressive MS" terminology, ICER conflates primary progressive multiple sclerosis (PPMS) with SPMS, which are distinct MS phenotypes with differing natural histories. By definition, PPMS is not a relapsing form of MS, although relapses can occur rarely,[1] and is typically an aggressive form of disease with continuous deterioration. SPMS, on the other hand, occurs subsequent to relapsing-remitting multiple sclerosis (RRMS) as the disease transitions from a more inflammatory phase to a more progressive phase. Clinical trial data of disease modifying drugs (DMDs) provide further support for the distinction between PPMS and SPMS: fingolimod had no clinical effect in PPMS,[2] yet siponimod – a product nearly identical in mechanism of action – has shown efficacy in SPMS.[3]

How ICER defines their population of interest will have significant implications for the appropriate comparators that should be included in the analysis. Many currently marketed DMDs are approved for relapsing forms of MS, which would include patients with SPMS, so long as they have relapses. However, the definition of 'relapsing MS' excludes those patients with SPMS in which relapses are no longer occurring (advanced stage of the disease with continuous deterioration). As siponimod's EXPAND trial primarily enrolled a non-relapsing SPMS population (n=1430 vs. n=215),[3] we do not believe that DMDs with an indication of relapsing MS are appropriate comparators for this analysis.

***Recommendations**:*

(a) Given that ICER's decision question is focused on siponimod's value in SPMS, ICER should evaluate DMDs that are used in SPMS specifically, not progressive MS generally.

(b) ICER should not limit its review to relapsing SPMS only but consider the entire SPMS population. DMDs with an indication in relapsing MS only should be excluded from this analysis, unless significant real-world data supports their use in the entire SPMS population (see next section).

2. Comparator selection based on demonstration of efficacy and utilization

ICER states that they will include comparators with "some efficacy" in progressive MS. We have concerns that ICER has not precisely defined their criteria for establishing "some efficacy". For

example, glatiramer acetate showed a modest, non-significant trend toward efficacy in PPMS in the PROMiSe study,[4] yet it is not included in ICER's list of comparators. Similarly, if the scope is to include DMDs that have shown "some efficacy" in any form of progressive MS, fingolimod should also be included in this review: while the INFORMS study evaluating fingolimod in PPMS was negative on its primary endpoint of time to 3-month confirmed disability progression, there was evidence of MRI efficacy.[1]

On the other hand, interferon beta-1a has only shown equivocal efficacy in SPMS. Interferon beta studies conducted in various stages of SPMS have yielded mixed results and therefore lack substantial evidence supporting an approved indication.[5,6,7] Subcutaneous interferon beta-1a was studied in patients with SPMS in the SPECTRIMS trial. In this population, no effect on disability progression was seen, although beneficial effects on relapse rates and MRI outcomes were observed.[8]

Furthermore, interferon beta-1a is not typically used in patients with SPMS.[9] A prospective chart review based on 101 private practices in the United States, presented at the 2013 ISPOR European Congress, indicated that patients with SPMS are treated with interferon beta-1b, glatiramer acetate, fingolimod, and natalizumab, with interferon beta-1b and glatiramer acetate typically being used in first or second line treatment, and fingolimod and natalizumab dominating third and later lines of treatment. A more recent survey of 101 United States neurologists indicate that up to 20% of all ocrelizumab prescriptions are for patients with SPMS.[10]

Given these considerations, ICER should more precisely specify how they arrived at their comparator list for this review. We would recommend ICER consider the following criteria for comparator inclusion:

- FDA label for SPMS specifically, **OR**
- Efficacy demonstrated in SPMS on the endpoint of confirmed disability progression (allowing for multiple possible definitions of disability, e.g. as measured by EDSS, or upper limb function, etc. See point 4), which is the most relevant efficacy measure in progressive forms of MS. **OR**
- Real-world evidence of significant utilization in SPMS

By these criteria, ICER's comparator list for this assessment would include glatiramer acetate, fingolimod, and ocrelizumab (based on real-world utilization); mitoxantrone (based on SPMS indication); and interferon beta-1b and natalizumab (based on real-world utilization and demonstration of efficacy on confirmed disability progression).

***Recommendation**: ICER should clarify how "some efficacy" is defined, base this definition on rigorous and consistent criteria, and remove therapies (such as interferon beta-1a) that do not meet this definition.*

3. Study Inclusion Criteria

ICER proposes to include studies of "at least 3 months duration" in their assessment. This criterion is problematic given the main endpoint of interest in the assessment will be EDSS progression confirmed at 3 or 6 months. A 3-month study would be too short to provide any information on EDSS progression. Studies assessing disability progression in this population are typically 2 years in duration or longer.[3,11,12]

***Recommendation**: ICER should include only studies with a duration of at least 2 years in their assessment.*

4. Analysis Endpoint

ICER proposes to use disability progression as a key endpoint in its analysis. Patients with SPMS may be ambulatory only with assistance, or wheelchair-bound, and in these populations, certain measures of disability progression (e.g. timed 25-foot walk test, or the EDSS scale which emphasizes ambulation) may not be as relevant to the patient as other measures (e.g. 9-hole peg test). We would therefore request that ICER clarify how they intend to measure disability progression in their analysis.

***Recommendation**: ICER should clarify how disability progression is being measured as an outcome in their analysis, and consider including disability progression measures likely to be most relevant to patients – for example, those such as the 9-hole peg test measuring manual function.*

We hope that you take our suggestions under advisement. Thank you again for the opportunity to provide our thoughts and recommendations on this draft scoping document.

Sincerely,
EMD Serono, Inc.

References

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Genentech
A Member of the Roche Group

November 20, 2018
Institute for Clinical and Economic Review (ICER)
2 Liberty Square
Boston, MA 02109

Dear ICER Review Panel,

Genentech is a leading biotechnology company that discovers and develops medicines to treat patients with serious or life-threatening medical conditions.

Multiple sclerosis (MS) is a chronic, disabling disease of the central nervous system that affects an estimated 400,000 people in the United States. There is no cure for MS. Patients with MS experience a wide range of symptoms, including muscle weakness, fatigue and difficulty seeing, that eventually lead to disability. Most people with MS experience their first symptom between 20 and 40 years of age, making the disease the leading cause of non-traumatic disability in younger adults. An important goal of treating MS is to reduce disease activity as soon as possible to slow how quickly a person's disability progresses.

Ocrelizumab, a humanized monoclonal antibody that selectively depletes CD20+ B cells, has demonstrated safety and efficacy in three Phase III randomized controlled trials. Approved by the FDA in 2017, ocrelizumab is the first and only approved disease-modifying therapy for both relapsing (RMS) and primary progressive (PPMS) forms of MS.

We highlight two key recommendations for your consideration in the upcoming review of disease-modifying therapies for secondary progressive multiple sclerosis (SPMS):

1. Rituximab should be excluded from this review due to its lack of FDA approval and insufficient evidence to support real-world utilization and clinical decision making in MS.
2. ICER should consider and account for differences in patient populations represented in the pivotal trials of the therapies that are proposed for inclusion in this review.

We further expand to provide additional details supporting our key points.

1. **Rituximab should be excluded from this review due to its lack of FDA approval and insufficient evidence to support real-world utilization and clinical decision making in MS.**

Health care policy and treatment decisions should be informed by evidence. The inclusion of rituximab in a clinical and economic review in SPMS is not valid or supported by robust clinical evidence. It is inappropriate to include rituximab for the following key reasons:

- There is no Class Ia evidence to support a rigorous evaluation of rituximab's efficacy, safety and cost-effectiveness in any MS population.
- Rituximab has not been investigated in any blinded randomized controlled trials that included SPMS patients. It has only been studied in one Phase II/III placebo-controlled trial in PPMS (OLYMPUS), which did not meet its primary endpoint of 12-week confirmed disability progression.[1]
- There is limited evidence to support that rituximab is used to treat SPMS patients in real-world clinical practice. Based on the Adelphi Multiple Sclerosis Disease Specific Programmes VII (Q1 2018), only 2 patients in the sample (n=122) were identified as having received Rituximab for non-FDA approved use in SPMS patients.[2]
- Rituximab is not currently being investigated or pursuing any indications in MS.
- As ICER concluded in their prior review, the evidence on rituximab in PPMS and RRMS was deemed inconclusive and given a rating of P/I.[3] There has been no change in the clinical evidence base of rituximab in MS since ICER's prior review. ICER will therefore draw similar conclusions for rituximab in SPMS.

ICER's inclusion of rituximab as a comparator implies that there is sufficient evidence to regard it as a viable treatment option in SPMS, a disease area where it is not being investigated and does not have FDA approval. Genentech strongly recommends that rituximab be excluded from this review due to the lack of robust scientific data.

2. **ICER should consider and account for differences in patient populations represented in the pivotal trials of the therapies under review.**

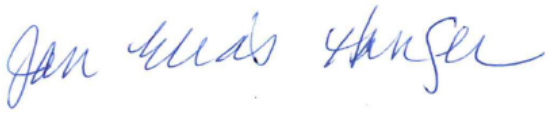
There is an emerging consensus that progression exists on a spectrum in MS. Given differences in patient populations between siponimod in the EXPAND trial and the ocrelizumab pivotal trial data, a valid comparison of the two therapies is methodologically challenging.[4,5] Genentech recommends the use of rigorous scientific evidence to inform treatment decisions.

- Populations characterized by their clinical course, as defined in clinical studies, will have different demographic and clinical profiles that limit comparative analyses.

- Differences in the baseline distribution of other demographic, clinical characteristics, and MRI markers of disease activity may similarly confound comparisons across treatments.
- It is consistent with best practices to acknowledge and appropriately account for these differences in any indirect treatment comparison.[6]

We welcome the opportunity to have a robust scientific discussion during the conduct of ICER's review in SPMS. We provide these comments with the intent to yield a comprehensive assessment that appropriately accounts for the strengths and limitations of current evidence, ensures patients' access to the therapies that they need, and represents the interests of all health care stakeholders.

Sincerely,



Jan Elias Hansen, Ph.D.
Vice President, Evidence for Access Medical Unit
Genentech US Medical Affairs

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National
Multiple Sclerosis
Society

November 20, 2018

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Via electronic mail: publiccomments@icer-review.org

Re: Draft Scoping Document for ICER Review of Siponimod for the Treatment of Secondary Progressive Multiple Sclerosis: Effectiveness and Value

The National Multiple Sclerosis Society (Society) appreciates the opportunity to submit comments on The Institute for Clinical and Economic Review's (ICER) *Draft Scoping Document for ICER Review of Siponimod for the Treatment of Secondary Progressive Multiple Sclerosis: Effectiveness and Value*. The Society works to provide solutions to the challenges of multiple sclerosis (MS) so that everyone affected by this disease can live their best lives. To fulfill this mission, we fund cutting-edge research, drive change through advocacy, facilitate professional education, collaborate with MS organizations around the world, and provide services designed to help people affected by MS move their lives forward.

MS is an unpredictable, often disabling disease of the central nervous system that disrupts the flow of information within the brain, and between the brain and body. The most common disease course, relapsing remitting MS (RRMS) is characterized by clearly defined attacks of new or increasing neurologic symptoms, followed by periods of partial or complete recovery. Approximately 85 percent of people with MS are initially diagnosed with RRMS. Secondary Progressive MS (SPMS) follows an initial relapsing-remitting course, and most people who are diagnosed with RRMS will eventually transition to a secondary progressive disease course in which there is a progressive worsening of neurologic function and accumulation of disability over time. SPMS can be further characterized at different points in time as either active (with relapses and/or evidence of new MRI activity) or not active, as well as with progression (evidence of disease worsening on an objective measure of change over time, with or without relapses) or without progression[i].

Each clinical course of MS presents and progresses differently in every individual. A growing body of evidence indicates that early and ongoing treatment with an FDA approved disease modifying therapy (DMT) is the best way to modify the course of the disease, prevent the accumulation of disability, and protect the brain. There are currently over 14 DMTs available to people with RRMS, and there are multiple variables that go into decision making for the use of these DMTs. While mitoxantrone received FDA approval for chronic progressive MS, a description that is no longer used, it is not commonly used in the treatment of SPMS due to toxicity concerns. **This was noted in the draft scoping document and the Society supports ICER's decision to not include it as a comparator treatment.**

Background: ICER's background information details that MS is "grouped into relapsing and progressive phenotypes" and discusses the classification of MS both in research and the clinical setting. We suggest that ICER review the 2014 Lublin et. al review that defines the clinical course of MS for communication, prognostication, design and recruitment of clinical trials, and treatment decision-making and the 2017 revision of the McDonald criterial for the diagnosis of MS for use in

research and clinical practice[ii]. **These are separate classification methods with different uses and we suggest that ICER acknowledge that and utilize those definitions appropriately in the final scoping document.** As noted in the McDonald revision, at the time of diagnosis, a provisional disease course should be specified (relapsing-remitting, primary progressive, or secondary progressive) and whether the course is active or not, and progressive or not based on the previous year's history. The phenotype should be periodically re-evaluated based on accumulated information. This recommendation is an addition to the 2010 McDonald criteria.[iii]

SPMS cannot be diagnosed outside of clinical observation, and in reality, is a retrospective diagnosis characterized by looking back at relapses, disease progression, clinical observations and patient reported outcomes and quality of life issues.

Scope: ICER states that evidence will be abstracted from randomized controlled trials (RCTs) as well as high-quality systematic reviews; high-quality comparative cohort studies, and input from patients and patient advocacy organizations, regulatory document data, and manufacturers information. However, as there are no head to head controlled randomized studies for SPMS over a sufficient length of time to establish definitive effects on the MS disease course, we urge ICER to address how they will address this significant gap in its review in its final scoping document.

Any clinical and economic review should reflect the current standard of care for people with SPMS. The Society encourages ICER to consider all available evidence around DMT usage in the current standard of care for SPMS in addition to what is measured in the siponimod trial (if there are differences). We know that current standard of care for SPMS includes the full range of DMTs.

Analytic Framework: The Society is concerned with the accuracy of the model that is proposed in the scoping document, using the interventions listed. Given that there is limited evidence of selected outcomes on SPMS, we are concerned that the proposed model will not reflect the reality of SPMS disease management.

Populations: The Society is concerned that the "newly diagnosed" population that ICER has targeting in the draft scoping document. We believe this diagnosis would be difficult to ascertain with any level certainty. While we know that most people diagnosed with RRMS will transition to SPMS, no biomarker currently exists to pinpoint the point of transition. Studies indicated that 50 percent of those diagnosed with RRMS will transition to SMPS within 10 years, and 90 percent would transition within 25 years.[iv] However, it must be noted that these assumptions are based on a natural history study that predates the introduction of DMTs. It remains an open question as to how DMTs affect the transition from RRMS to SPMS and studies are lacking that examine the impact DMTs on natural history of the disease.

A variety of strategies are utilized by physicians to determine if an individual with RRMS has transitioned to SPMS, including neurologic examinations, a review of symptom history, and magnetic resonance imaging (MRI) scans. Additionally, many physicians are hesitant to diagnose SPMS because of potential impacts on treatment. **Due to these complications, the Society believes that the appropriate population for this review would be anyone who is eligible to initiate treatment for SPMS and we urge ICER to avoid using the term "newly diagnosed" in its final scoping document.**

Further, the draft scoping document states that "if data permit, we will examine heterogeneity of treatment effect across subgroups stratified by age, disease duration, disease activity, relapse history and level of disability." The Society believes ICER should acknowledge the assumptions and

limitations of this data when making any recommendations, as the ICER's assumptions which may not reflect reality of SPMS disease management.

Comparators: The Society recommend that ICER detail the sources of the evidence that they will be utilizing in their review in their final scoping document. To our knowledge, the data for safety and efficacy of treatments for SPMS is severely limited.

Potential Other Benefits and Contextual Considerations: While we have had promising conversations to date, the Society strongly urges ICER to utilize patient engagement to gather evidence and data on other potential benefits and contextual considerations. It is critical that the ICER's review reflect the real-life experiences, perspectives, hopes and concerns of people living with MS. Many of these aspects inform healthcare decision making and must be incorporated into the review. The Society recommends that ICER partner with MS stakeholders on patient engagement endeavors that will provide data and context to inform this important section of the review and detail how the data obtained will be used within or to inform ICER's model.

Scope of Comparative Value Analyses: As ICER considers the inputs into building the model, we encourage you to have in depth conversations with the MS community about what evidence and studies exist to inform the model. Additionally, we encourage ICER to consider the price of current disease-modifying therapies in its comparative value analysis. We know that most people diagnosed with RRMS will transition to SPMS. As this transition is more blurred than a clear delineation and many current DMT labels include a broad "relapsing" characterization, many people who might be described as SPMS are currently, or were until very recently, on a DMT. Accounting for this in cost effective and comparative value analyses will be more reflective of what is currently happening in the treatment and care of people with SPMS.

Identification of Low-Value Services: The final scoping document should include examples of services that ICER views are low-value, as the definition in the draft scoping document is very vague. There must be criteria to determine whether an item is a low value service. We urge caution in using this language because of real world impacts on people with MS.

Thank you for the opportunity to comment. If you have any questions, please contact Leslie Ritter, Senior Director, Federal Government Relations at leslie.ritter@nmss.org or 202-408-1500.

Thank you,

Bari Talente, Esq.
Executive Vice President, Advocacy

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Novartis appreciates the opportunity to participate in ICER's review of siponimod (BAF312) for secondary progressive multiple sclerosis (SPMS). Siponimod, an investigational agent that is currently under FDA review, is a selective sphingosine-1-phosphate (S1P) receptor modulator that is taken as an oral tablet once daily. Novartis has a long-standing history in neuroscience, and we are dedicated to continued innovation in supporting patients throughout their treatment journey, which is reinforced through our ongoing research on new therapies to treat both relapsing and progressive forms of MS. SPMS affects an estimated 20–26%[1,2] of the 400,000 MS patients in the United States.[3] Given the substantial burden that SPMS imposes on patients and their caregivers,[1,4-8] siponimod may substantially improve the lives of patients by reducing accumulated disability.[9] With this commitment to patients and innovation in mind, we submit the following comments on the draft scoping document posted on October 31, 2018. Novartis believes that incorporating the recommendations below will make ICER's evaluation of siponimod more thorough, accurate, and balanced. We are hopeful that this evaluation will ultimately support patient access to the first oral disease modifying therapy (DMT) with the potential to delay SPMS progression.

Population

ICER's cost-effectiveness model should apply a societal perspective to measure siponimod's full value

Failing to measure the impact of SPMS on work productivity and other indirect costs in the baseline model biases the baseline estimates towards lower cost-effectiveness. Furthermore, ICER should include caregiver time cost and disutility in the cost-effectiveness model, as has previously been done by National Institute for Health and Care Excellence (NICE) in assessments of relapsing-remitting MS (RRMS).[10-13] The burden of MS on patients and caregivers is large;[7,14-20] in one study, 40.9% of caregivers provided more than 20 hours of care per week.[20] Further, ICER's approach does not account for other key components of value including, but not limited to: (1) patient satisfaction, (2) functional status, and (3) societal value of innovation (e.g., "insurance value" ascribed to treatment from the perspective of individuals without MS).[17,21,22]

SPMS should be defined as a progressive increase in disability independent of relapses

As noted in the draft scoping document, distinguishing the SPMS patient population from the relapsing-remitting multiple sclerosis patient population can be challenging. ICER must define the cohort in its analysis so that it represents the true SPMS population. The SPMS population consists of patients who experience a progressive increase in disability for at least 6 months independent of relapses.

Comparators

The comparators in ICER's assessment should correspond to treatments used in the real world for SPMS. Novartis agrees with ICER's position that mitoxantrone is not a relevant comparator because it is rarely used in clinical practice due to its risk/benefit profile.

Best supportive care is not an appropriate comparator given the current treatment landscape

As stated above, comparators should reflect real-world utilization of DMTs in SPMS patients. Novartis has submitted data on real-world treatment utilization in the SPMS patient population,

including those with active or non-active disease, under separate cover,[23] as commercial-in-confidence data. Given the real world utilization of DMTs in the SPMS patient population, best supportive care (BSC) is not a relevant treatment option, especially for those newly diagnosed with SPMS, or those initiating treatment for SPMS.

Rituximab is also not an appropriate comparator

First, rituximab has no indication for any MS phenotype,[24] and it has limited efficacy and safety data in MS populations.[25,26] A Cochrane Review's NMA concluded that: "There is not sufficient evidence to support the use of rituximab as a [DMT] for RRMS."[27] The only comparative trial of rituximab included in the NMA was cited as high risk of bias due to high attrition.[25] This study was not sufficiently powered to detect changes in important endpoints such as relapses, brain volume loss, and safety. Off-label use of rituximab may have public safety consequences, particularly in light of boxed warnings and reported data on serious adverse events for on-label indications.[24] Therefore, its inclusion as a comparator is inappropriate in this assessment. The lack of information on rituximab also complicates indirect treatment comparisons. Second, as stated above, selected comparators should have utilization rates that correspond to real-world experience for DMTs used by patients with SPMS. While rituximab use in MS patients is not uncommon, recent estimates show utilization is not only low, but also decreasing in the SPMS population,[28] which may be driven by the introduction and widespread uptake of ocrelizumab. Rituximab and ocrelizumab are both monoclonal B-cell depleting anti-CD20 antibodies, and while they target the same protein, rituximab is chimeric and ocrelizumab is humanized. Ocrelizumab has been studied more thoroughly and rigorously, and as a result, it is indicated for both relapsing multiple sclerosis (RMS) and primary progressive multiple sclerosis (PPMS) populations.[29]

Consider a matched adjusted indirect treatment comparison analysis

Comparing siponimod to other therapies commonly used by SPMS patients is complicated by differences in clinical trial study design and populations. Only three other DMTs (natalizumab, interferon beta-1b, and mitoxantrone) have been studied specifically in SPMS populations.[30-34] However, the patients included in the interferon studies are considerably different than the patients in EXPAND, reflecting differences in both demographics and the time separating the periods when the two studies were conducted. For the interferons, only one study has shown superiority relative to placebo among SPMS patients[35] and this study focused on a population with earlier disease and lower EDSS scores than the EXPAND population. The ASCEND natalizumab study population[30] is similar to EXPAND, but definitions for disease progression differ. The other comparators (rituximab, ocrelizumab) have no published efficacy or safety data from randomized clinical trials (RCTs) specific to SPMS populations. A propensity-matched cohort study of 1,378 SPMS patients with similar patient characteristics to EXPAND found no DMT disability progression benefits, compared to untreated patients.[36] Siponimod is the first DMT to demonstrate an impact on disability progression in the population of interest in a clinical trial setting.

Novartis anticipates it is possible to construct a network from the published SPMS studies for indirect comparison but the network is too small to enable adjustment through meta-regression. This means that point estimates derived from a network meta-analysis (NMA) are not consistently plausible from a clinical perspective. There are also methodological issues with an NMA approach as there are several different placebos within the network. For these reasons,

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Novartis believes that a series of pairwise matched-adjusted indirect comparisons using individual patient data from EXPAND offers the most methodologically accurate option for addressing differences in study population characteristics.

Clarify the base-case scenario

Please clarify what the base-case comparison will be, and how it will be chosen. Specifically, will siponimod be compared head-to-head in a pairwise fashion to all individual comparators listed in the scoping document, or will the comparator consist of a market basket? If the former, which individual head-to-head comparison will be considered the base case? How will that comparator be chosen? If the latter, how will the distribution of comparators in the market basket be determined? For either approach, we once again recommend the base-case comparison represent real-world utilization of DMTs in this population.

Outcomes

Clarify how MRI disease activity will be measured and quantified, and consider inclusion of brain atrophy as an outcome in its place

Please clarify how MRI disease activity will be measured and quantified and why it is considered an intermediate outcome. We believe that MRI activity, such as gadolinium (Gd) enhancing lesions, is not a correct marker for disease progression. Gd lesions have the lowest correlation in disease progression as it is demonstrating whether the person has inflammatory activities on the day and time the MRI was taken. Many Gd lesions appear and disappear and thus are not great correlates to disease progression or disability accumulation. We recommend the assessment of brain atrophy as an MRI surrogate marker for disability progression as this is highly correlated with disability progression.[37] In EXPAND, siponimod patients experienced 0.18% less brain volume reduction 12 months after baseline compared to patients on placebo ($p<0.0001$).[9]

Closing remarks

Novartis would like to express gratitude to ICER for the opportunity to collaborate and participate in the review of siponimod for SPMS, and appreciates your consideration of our comments. We are committed to providing safe and efficacious treatments for patients in all stages of MS. Given the limited treatment options for patients with SPMS, careful consideration of the unique challenges and contextual issues of developing a value-based model is central to conducting a relevant and informative value assessment. We look forward to partnering with ICER to facilitate an accurate and balanced value assessment of siponimod, based on rigorous science and the best available evidence.

Sincerely,

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