



April 10, 2019
Institute for Clinical and Economic Review
2 Liberty Square
Boston, MA 02109

Dear ICER Review Panel,

Genentech appreciates the opportunity to respond to the ICER Secondary Progressive Multiple Sclerosis (SPMS) Draft Evidence Report. Genentech is committed to conducting the highest quality science and welcomes the discussion about the value of our medicines to patients, providers, society, and the health care system.

We are in agreement with ICER's characterization that progression in multiple sclerosis (MS) occurs on a spectrum, and that diagnosing the transition from relapsing remitting MS to the SPMS phenotype is challenging in both research and clinical settings. Despite similarities in the natural histories between relapsing MS and SPMS, we support the decision to omit direct comparisons of Siponimod to other therapies given substantial differences in the patient populations represented in the clinical trials.

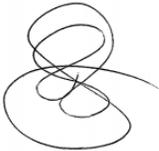
In addition, capturing outcomes important to patients is critical. MS is a debilitating disease that impacts patients in the prime of their lives, with a mean age of onset of 31 years in the US (range 17-50 years old).¹ The MS Coalition survey included in this report indicates there are meaningful patient outcomes with regard to quality of life improvements such as walking, fatigue, spasticity, balance, and hand function, which have not been adequately incorporated into the review.² While clinical trials in MS typically rely on global assessments of disability progression such as the expanded disability status scale (EDSS), the EDSS mostly assesses physical symptoms and is less sensitive to these manifestations of the disease. We believe ICER should include the following to provide a more accurate representation of the clinical benefit of Ocrevus to MS patients.

- Nine-hole peg test (9HPT) and timed 25-foot walk (T25-FW)
 - The Phase 3 ORATORIO trial included exploratory endpoints which were presented in the appendix of the publication. Specifically, the T25-FW and 9HPT, endpoints that measure lower and upper extremity function, were included and are particularly important in the progressive MS patient populations. In particular, on page 12, Table S4A and S4B illustrate the observed effect of Ocrevus on the time to onset of 12- and 24-week confirmed >20% progression in T25-FW and 9HPT as compared to placebo.³

- An exploratory analysis of the ORATORIO trial exploring the effect of Ocrevus on reducing the risk of upper extremity disability progression in patients with primary progressive MS compared to placebo has also been published.⁴
- Cognition (assessed by symbol digit modalities test (SDMT))
 - A pooled analysis of the OPERA I and II studies showed Ocrevus was associated with significant improvements vs. IFN β -1a in SDMT performance in patients with relapsing MS with or without moderate cognitive impairment.⁵

In closing, we thank you for the opportunity to comment on this draft evidence report. We believe these recommendations will yield a comprehensive assessment that better reflects the value of disease modifying therapies and accounts for the evidence needs of all healthcare stakeholders. We welcome the opportunity to further discuss our recommendations.

Sincerely,

A handwritten signature in black ink, appearing to be 'Jennifer Whiteley', written in a cursive style.

Jennifer Whiteley, EdD., MSc., MA
Head, Neuroscience/Rare Disease
Evidence for Access Medical Unit
Genentech, US Medical Affairs

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2. Institute for Clinical and Economic Review. Siponimod for the Treatment of Secondary Progressive Multiple Sclerosis: Effectiveness and Value. Draft Evidence Report (2019). Accessed March 22, 2019.
3. Montalban X, Hauser SL, Kappos L, et al. Ocrelizumab versus Placebo in Primary Progressive Multiple Sclerosis. *N Engl J Med*. 2017;376(3):209-220.
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April 10, 2019

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

Via electronic mail: publiccomments@icer-review.org

Re: Siponimod for the Treatment of Secondary Progressive MS: Effectiveness and Value

On behalf of the Multiple Sclerosis Coalition (MSC), thank you for the opportunity to comment on ICER's *Draft Evidence Report on Siponimod for the Treatment of Secondary Progressive MS*. The MS Coalition, founded in 2005, is a network of nine independent MS organizations dedicated to improving the quality of life for those affected by MS. Many people with MS, family members and healthcare providers who care for those with MS are connected to one or more members of the MS Coalition.

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.¹

The MS Coalition strongly urges ICER to discontinue the current review for siponimod. While we appreciate the time and resources ICER has devoted to this review, the FDA approval for siponimod and the subsequent approval for cladribine for "relapsing forms of MS to include relapsing-remitting and active secondary progressive MS" means the scope of the report is no longer sufficient. Specifically, we offer the following:

- The draft review only looks at part of the FDA-approved label for the product.
- The comparison of siponimod to supportive care is not reflective of current practice and will not describe practice moving forward. Given the FDA's recent writings, all drugs approved for the treatment of relapsing forms of MS can be used to treat active SPMS. Thus, the comparison to supportive care is inadequate and does not offer actionable information for people with MS, prescribers or payors.
- ICER will be unable to offer a price benchmark as the draft review looks only at part of the approved label.

Should ICER continue with the review despite the MSC's best advice, we provide the below comments on the draft report.

Insights Gained

The MS Coalition appreciates ICER's efforts to gain insight from patients and include these insights in the report. While ICER gained insights from both a survey with more than 3,000 respondents and a small focus group, we do caution ICER from believing that a single focus group of three provides substantial perspectives into the lives of those living with SPMS.

Comparative Clinical Effectiveness

It is clear ICER spent time and effort analyzing data from many sources. The clinical trial was designed and powered for the full SPMS population. While the FDA approval is for relapsing to include active SPMS, indicating the FDA looked at subgroup data, Coalition reviewers question the ability to undertake separate cost benefit analyses based on subgroup populations in the clinical trial.

Long-Term Cost Effectiveness

While ICER states there was insufficient evidence to compare siponimod to alternative disease modifying therapies, the MSC reiterates its statement from above that the comparison to best supportive care will not provide actionable information to people with MS, healthcare providers or payors based on the FDA's position that all medications approved for relapsing forms of MS include active SPMS. A comparison to best supportive care does not assist in decision making concerning the best path forward in the clinical setting.

MSC urges ICER to reevaluate several of its key model characteristics and assumptions. Notably, based on a label indication for active SPMS, discontinuation rates used in the model are likely too low. Treatment will be utilized during active SPMS and not throughout the entire course of SPMS. Overall, the presumption of lifelong use of any DMTs does not reflect the current clinical practice in which older MS patients may discontinue use of DMTs and research is underway to understand the pros and cons, as well as timing of treatment discontinuation. Additionally, ICER should reevaluate the cycle length of one year. Several MSC reviewers commented that an EDSS of 6 is a level at which the EDSS tends to stabilize for years.

Health Care Utilization Costs

The draft report states that relapses bring an additional mean annual direct cost of \$2,747 per relapse. This data point is from a survey of people with relapsing MS and the report does not explore if there are cost differences for relapses of people with SPMS vs. RRMS. A study published in 2015 found that ongoing relapses after the onset of progressive MS shortened the time to EDSS 6, increasing disability compared to relapses in RRMS.ⁱⁱ This indicates higher health care costs are likely associated with relapses in SPMS vs. RRMS.

Additionally, within the steps of the EDSS, there can be progression of disease not captured by the score (i.e. cognitive dysfunction, bladder symptoms, fatigue, pain). As these data are not reported, it raises questions as to capturing healthcare costs and quality of life that could impact effectiveness and value. It is also well known that direct healthcare costs do not fully reflect the economic burden of living with MS.

Other Comments

The MSC recognizes there are some differences between this review and others undertaken by ICER. The FDA label is different than some had anticipated and the approval of another MS DMT, also for relapsing MS including active SPMS occurred after the draft report was released. Given these changes to the therapeutic landscape based on when ICER began this review, we urge ICER to consider whether this report provides information that is timely, helpful and actionable to the MS community, healthcare providers and payors.

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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- ⁱⁱ Soldan, et al. Neurology. 2015 Jan 6;84(1):81-88. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4336097/>



National
Multiple Sclerosis
Society

April 10, 2019

Institute for Clinical and Economic Review

Two Liberty Square, Ninth Floor
Boston, MA 02109

Via electronic mail: publiccomments@icer-review.org

Re: Siponimod for the Treatment of Secondary Progressive MS: 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 evidence report, *Siponimod for the Treatment of Secondary Progressive MS: Effectiveness and Value*. The Society works to provide solutions to the challenges of MS so that everyone affected by this disease can live their best lives.

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. A recently completed prevalence study, funded by the National MS Society, estimates that nearly 1 million people over the age of 18 live with MS in the United States. More than half are currently connected with the Society.

Secondary Progressive MS (SPMS) follows an initial relapsing-remitting course. Prior to the availability of approved disease-modifying treatments (DMTs), studies indicated that 50 percent of those diagnosed with RRMS would transition to SPMS within 10 years, and 90 percent would transition within 25 years. It is widely believed that DMTs have an impact on disease progression, but information is not yet available to determine the extent to which DMTs alter or delay the transition to SPMS. SPMS can be 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.¹

The Society strongly urges ICER to discontinue the current review for siponimod. While we appreciate the time and resources ICER has devoted to this review, the FDA approval for siponimod and the subsequent approval for cladribine for "relapsing forms of MS to include relapsing-remitting and active secondary progressive MS" means the scope of the report is no longer sufficient. Specifically, we offer the following:

- The draft review only looks at part of the Food and Drug Administration (FDA)-approved label for the product with the review exploring secondary progressive MS while the approved labeling is for relapsing forms of MS including RRMS, clinically isolated syndrome and active SPMS.
- The comparison of siponimod to supportive care is not reflective of current practice and will not describe practice moving forward. Given the FDA's recent writings, all drugs

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approved for the treatment of relapsing forms of MS can be used to treat active SPMS. This renders the comparison to supportive care inadequate and does not offer actionable information for people with MS, prescribers or payors.

- ICER will be unable to offer a valid price benchmark as the draft review does not examine the approved condition for siponimod.

Should ICER continue with the review, we provide the below comments on the draft report.

Insights Gained

The Society appreciates ICER's efforts to gain insight from patients and include these insights in the report. While ICER gained insights from both a survey with more than 3,000 respondents and a small focus group, we do caution ICER from believing that a single focus group of three provides substantial perspectives into the lives of those living with SPMS. Although insights may be gained from such a small group, one cannot generalize the perspectives of three individuals across all those living with SPMS.

Comparative Clinical Effectiveness

It is clear ICER invested considerable time and effort analyzing data from many sources. The clinical trial was designed and powered for the full SPMS population, yet ICER segments the population into subgroups. While we recognize it is likely the FDA performed subgroup analysis for efficacy, reviewers question the ability to undertake separate cost benefit analyses based on subgroup populations. From a rigor perspective, the subpopulation data is insufficient to perform comparative assessments.

Long-Term Cost Effectiveness

While ICER states there was insufficient evidence to compare siponimod to alternative disease modifying therapies, the Society reiterates its statement above that the comparison to best supportive care is inadequate and will not provide actionable information to people with MS, healthcare providers or payors based on the FDA's position that all medications approved for relapsing forms of MS include active SPMS. Moreover, a comparison to best supportive care does not assist in decision making concerning the best path forward in the clinical setting.

The Society urges ICER to reevaluate several of its key model characteristics and assumptions. Notably, based on a label indication for active SPMS, discontinuation rates used in the model are likely too low. Treatment will be utilized during active SPMS and not throughout the entire course of SPMS. Overall, the presumption of lifelong use of any DMT does not reflect the current clinical practice in which older MS patients may discontinue use of DMTs and research is underway to understand the pros and cons, as well as timing of treatment discontinuation. Additionally, ICER should reevaluate the cycle length of one year. Several reviewers commented that an EDSS of 6 is a level at which the EDSS tends to stabilize for years.

Health Care Utilization Costs

The draft report states that relapses bring an additional mean annual direct cost of \$2,747 per relapse. This data point is from a survey of people with relapsing MS and the report does not explore if there are cost differences for relapses of people with SPMS vs. RRMS. Generalizing

this cost to the SPMS population is likely not valid. In fact, a study published in 2015 found that ongoing relapses after the onset of progressive MS shortened the time to EDSS 6, increasing disability compared to relapses in RRMS.ⁱⁱ This indicates higher health care costs are likely associated with relapses in SPMS vs. RRMS.

Additionally, within the steps of the EDSS, there can be progression of disease not captured by the score (i.e. cognitive dysfunction, bladder symptoms, fatigue, pain). As these data are not reported, it raises questions as to capturing healthcare costs and quality of life that could impact effectiveness and value. It is also well known that direct healthcare costs do not fully capture the burden of disease.

Other Comments

ICER should utilize alternatives to the Quality Adjusted Life Year

The Society has previously recommended that ICER should clarify its calculation of the quality adjusted life year (QALY), particularly as there are concerns that a cost-per-QALY cannot adequately account for the value of substantially improving the life of a person with a disability or serious medical condition. ICER should examine both alternative approaches and health utilities such as disability adjusted life years, which may enable payers to develop policies that better reflect individual patient values.

The Society recognizes there are some differences between this review and others undertaken by ICER. The FDA label is different than some had anticipated and the approval of another MS DMT, also for relapsing MS and including active SPMS occurred after the draft report was released. Given these changes to the therapeutic landscape based on when ICER began this review, we strongly urge ICER to consider whether this report provides information that is helpful and actionable to the MS community, healthcare providers and payors.

Thank you for the opportunity to comment on behalf of the more than 530,000 people with MS currently connected with the National MS Society. If you have any questions, please contact me at bari.talente@nmss.org or 202-408-9485.

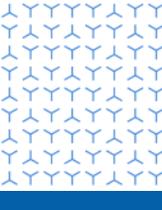
Sincerely,



Bari Talente
EVP, Advocacy

ⁱ Lublin, et al. Neurology. 2014 Jul 15;83(3):278-86. doi: 10.1212/WNL.0000000000000560. Epub 2014 May 28. <https://www.ncbi.nlm.nih.gov/pubmed/24871874>

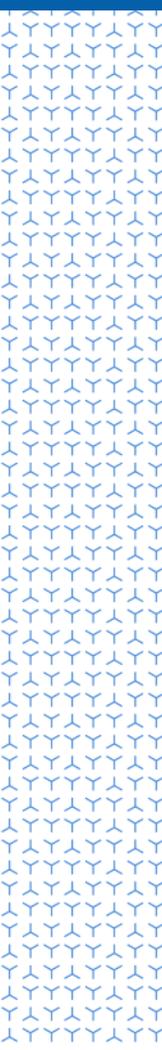
ⁱⁱ Soldan, et al. Neurology. 2015 Jan 6;84(1):81-88. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4336097/>



Response to ICER's Draft Evidence Report for the Assessment of Siponimod for Secondary Progressive Multiple Sclerosis

Novartis Pharmaceuticals Corporation

April 10, 2019



1@novartis.com

Primary contact:
Vivian Herrera
Vice President and Head HE&OR
Novartis Pharmaceuticals Corporation
Email: vivian-1.herrera@novartis.com

Novartis appreciates the opportunity to provide feedback to ICER on the Draft Evidence Report of siponimod for the treatment of Secondary Progressive Multiple Sclerosis (SPMS). In this response, we provide recommendations to ensure that the clinical and economic value of siponimod is accurately captured and described in the Revised Evidence Report.

On March 26, 2019, the US Food and Drug Administration approved siponimod for the treatment of relapsing forms of multiple sclerosis, including clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults.^{1,2} Given the substantial burden that SPMS imposes on patients and their care partners,³⁻⁸ siponimod may improve the lives of patients by slowing disability progression and frequency of relapse.⁹ Siponimod is unique to currently available S1P modulator DMTs in its specificity for S1P₁ and S1P₅ receptors, resulting in peripheral anti-inflammatory effects and direct effects on the central nervous system. Further, siponimod is also the first and only drug with proven efficacy in delaying disability progression in a representative SPMS patient population. Siponimod's phase III EXPAND trial was the largest controlled clinical study of SPMS patients, showing siponimod significantly reduced the risk of disease progression, as well as favorable reductions in annual relapse rate and MRI measures of inflammatory disease activity.⁹

Based on our review of the ICER siponimod Draft Evidence Report and the economic model provided by the University of Washington, we submit the following recommendations. We believe these recommendations will further enhance the evidence-based clinical and economic review of siponimod to more accurately represent the real-world clinical context and evidence base for treatment of SPMS.

Population

ICER should consider the full evidence base for MS prevalence in the United States

Secondary Progressive Multiple Sclerosis is a progressive neurological disease affecting an estimated 25%¹⁰ of the approximately 400,000–500,000 MS patients in the United States.^{11,12} A recently published study reported the prevalence of MS may be as large as 913,925, however, this estimate is driven largely by a number of inflation factors to upwardly adjust the observed prevalence in the study of 470,053.¹³ This single study should be considered alongside the full evidence base for previously published MS prevalence estimates and ICER should consider a range of prevalence estimates.

ICER should evaluate the clinical and economic value of siponimod in a SPMS population.

Novartis believes that siponimod should be evaluated based on the population studied in the phase III randomized clinical trial (EXPAND).⁹ While Novartis understands the desire to match the clinical and economic evaluation with the label granted by the FDA, siponimod remains to be the only oral DMT with proven efficacy in the SPMS population. It should also be noted that the EXPAND trial was not powered to assess efficacy in active and non-active SPMS patient subgroups.

ICER should not model the economic value for patients with active and non-active disease separately.

ICER has acknowledged that it can be difficult to distinguish RRMS patients and those transitioning to SPMS. It can be even more difficult to assess active and non-active SPMS patients in the real world. Active disease is defined by Lublin as the presence of relapses (new or increasing neurologic dysfunction followed by full or partial recovery) and/or the occurrence of contrast-enhancing T1 hyperintense or new or unequivocally enlarging T2 hyperintense lesions.¹⁴ However, while presence of disease activity can identify a patient as being active, a patient that is still experiencing disease activity can be misclassified as non-active. In the real-world, the timing of relapses are variable, and if a patient does not experience a relapse over, for example, a two year period, it may be difficult to discern if this is due to the effect of treatment with a disease modifying therapy (DMT), the variability of time between relapses (i.e., the time period is not long enough to observe a relapse), or the patient is transitioning to non-active SPMS. In the EXPAND trial, a two year look-back period was used to characterize patients as active (those that experienced a relapse in the prior two years) or non-active (those that did not experience a relapse in the prior two years).⁹ This two-year look-back period was somewhat arbitrary and was chosen to facilitate the execution of the trial. In fact, in the placebo arm of EXPAND there were patients classified as non-active at baseline who experienced a relapse during the study period. This has also been observed in the real-world: a recent survey of more than 200 clinicians found that patients initiating DMT and characterized as having non-active SPMS still experienced relapse in the prior 12 months.¹⁵ By maintaining SPMS as the population of interest, consistent with the population assessed in the phase III EXPAND clinical trial, Novartis believes that the ICER evaluation will more accurately reflect real-world, stakeholder-relevant conditions and will therefore maximize the clinical relevance and meaningfulness of their review to stakeholders.

Comparators**In the economic evaluation, siponimod should be compared to disease modifying therapies to more accurately reflect real world clinical practice and the SPMS patient experience.**

Novartis appreciates the intention of ICER to compare siponimod to other available DMTs (ocrelizumab, natalizumab, and beta interferons) in both the clinical effectiveness and economic evaluation. For both exercises, ICER concluded that given lack of head-to-head data and the inability to indirectly compare siponimod to other DMTs, siponimod could only be compared to Best Supportive Care (BSC). Novartis feels strongly that the comparators in ICER's economic assessment should correspond to real-world clinical practice and treatment guidelines for MS.¹⁶ The American Academy of Neurology (AAN) treatment guidelines recommend that "people with SPMS who have relapses or active MRI-detected new lesion formation benefit from DMT."¹⁶

Additionally, excluding other DMTs from the cost effectiveness model questions the validity of ICER's results, as they will not reflect real-world clinical practice and the SPMS patient population currently managed by providers and payers. The Multiple Sclerosis Coalition's survey of 3,352 patients included in the siponimod Draft Evidence Report found that the minority (37%) of respondents who self-reported an SPMS diagnosis reported using no treatment (i.e., 63% of patients reported receiving treatment with a DMT). Given the challenges in identifying and subsequently formally diagnosing a patient as having SPMS, this estimate may be an overestimation of the untreated SPMS patients. Further, given the clinical course of MS, it

is likely that untreated patients have non-active SPMS. Market research previously submitted by Novartis to ICER as commercial-in-confidence¹⁷ suggests that approximately 75% of SPMS patients are treated with a DMT, further underscoring that BSC is not a representative comparator for the majority of SPMS patients.

Another important consequence of excluding DMTs as comparators is that the health system perspective used in the assessment of cost effectiveness will not accurately capture real-world costs of active treatment with DMTs. Current clinical practice is to use DMTs indicated for relapsing forms of MS to treat SPMS patients who continue to experience disease activity, especially in the early clinical course of SPMS. Thus, when SPMS patients are prescribed DMTs, the health system incurs costs for active treatment in this patient population, despite the fact that DMTs such as natalizumab and interferons do not have proven efficacy in the ability to slow disease progression in the SPMS population.^{18,19}

In the absence of publicly available head-to-head estimates of comparative efficacy, the matched-adjusted indirect treatment comparison estimates submitted by Novartis should be used in the base case assessment of the cost effectiveness of siponimod.

Novartis acknowledges that indirectly 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.^{18,20-23} However, the patients included in the interferon studies are considerably different than the patients in EXPAND,⁹ reflecting differences in both demographics and the time separating the periods when the two studies were conducted. The ASCEND natalizumab trial¹⁸ with similar study population to EXPAND and differing definitions for disease progression, did not demonstrate efficacy in relation to the primary endpoint. The other ICER comparator of interest, ocrelizumab has no published efficacy or safety data from randomized clinical trials specific to SPMS populations.

In order to perform a value assessment, comparison across clinical trials is typically undertaken. There are methodological issues when implementing a network meta-analysis (NMA) approach, particularly when the network is small. Therefore, point-estimates derived from such an analysis may produce results that are not consistently plausible from a clinical perspective. To address the need to reflect real-world DMT utilization, Novartis conducted a series of pairwise matched-adjusted indirect comparisons (MAICs) using individual patient data from EXPAND. This approach offers the most methodologically acceptable, most accurate option for addressing differences in study population characteristics.

Novartis is aware there may be a perception of bias in our interest to have an MAIC conducted. However, the analysis has been conducted with the principle of most conservative assumption in order to address this perception. In our approach, we achieved notable narrowing of confidence intervals after completing comparison of siponimod to interferon beta (Betaseron, Rebif, Avonex) and natalizumab (Tysabri). Novartis has previously shared the technical report with ICER in-confidence. Novartis feels strongly that ICER should consider the results of this approach when assessing the cost effectiveness of siponimod in the base case evaluation, rather than as a scenario, as this would more accurately represent real-world utilization of DMTs among SPMS patients. Thus, this approach would provide a more relevant and useful assessment of siponimod's value to stakeholders.

Furthermore, during the evaluation of the economic model provided by the University of Washington as part of ICER's Model Transparency Program, Novartis found that when siponimod is compared to BSC, no level of siponimod efficacy results in siponimod being deemed cost-effective. This finding underscores that, in addition to the need to accurately capture the real-world experience of SPMS patients, the cost-effectiveness model should include appropriate comparators so that the model will be relevant and useful to stakeholders.

Economic Model Inputs

The review of the economic model provided by the University of Washington revealed additional concerns. Novartis would like to provide the following feedback and recommendations.

Mortality

Novartis would like to bring to ICER's attention that the mortality table used in the model does not match the data in the Draft Evidence Report. Novartis suggests ICER update these data accordingly.

Relapse Rates

The Draft Evidence Report stated that a uniform relapse rate will be applied for each EDSS state corresponding to the baseline rates for the placebo arm of EXPAND, which are acknowledged to be lower than rates observed in other studies.^{24,25} Given the expectation that relapse rates will vary by EDSS state, Novartis suggests the use of annualize relapse rate per Bozkaya (2017).²⁵

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, and to support care partners and healthcare providers in all stages of MS. Careful consideration of the unique challenges of developing a value-based model is central to conducting a relevant and informative value assessment. We look forward to continued collaboration with ICER to facilitate an accurate and balanced value assessment of siponimod, based on rigorous science and the best available evidence.

Sincerely,

Vivian Herrera
Vice President and Head, US HE&OR
Novartis Pharmaceutical Corporation
Email: vivian-1.herrera@novartis.com

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Where legally able (as copyright and data embargos permit), Novartis is happy to share posters that are not available online after the conclusion of congresses.

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April 12, 2019

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

Dear Dr. Pearson:

Multiple sclerosis (MS) is an unpredictable and frequently disabling disease of the central nervous system. It disrupts the flow of information within the brain and between the brain and body. The most common disease course is relapsing remitting MS (RRMS), which is characterized by attacks of new or increasing neurological symptoms followed by periods of recovery. Secondary progressive MS (SPMS), which often follows RRMS, results in progressively worsening neurological function and disability and has very limited treatment options available to combat this debilitating disease.¹

The Institute for Clinical and Economic Review (ICER) recently released its draft evidence report for a treatment specifically for SPMS. We strongly agree with the National Multiple Sclerosis Society that ICER should discontinue the current review for siponimod due to the FDA approval for siponimod and the subsequent approval for cladribine for “relapsing forms of MS to include relapsing-remitting and active secondary progressive MS,” which means that ICER’s scope of the report is no longer sufficient. Additionally, the draft report, which was conducted at too early a point to have sufficient evidence on the treatment, also suffers from two other key shortcomings: the assessment does not consider patient and caregiver preferences and relies on outdated studies and data, calling ICER’s findings into further question.

ICER Data Suggests there are Health States Worse Than Death

ICER’s model includes data from a study that uses “negative utilities” *which implies ICER is assuming there are health states worse than death*. It is widely accepted that the logic of having negative utilities for any health state would lead to the contradictory goal of the premature death of a patient resulting in both health gain and being considered a cost-effective intervention. The use of these utilities shows a callous disregard for patients and an instinct to prioritize cost above all else, even with patient lives at stake. The use of such utilities, while failing to have comprehensive conversations with patients and caregivers about their preferences and what matters most to them in treatment, would skew how decision-makers value treatments and harm patient access to care.

¹ National MS Society. What is MS? Available at: <https://www.nationalmssociety.org/What-is-MS>

ICER's Assessment of MS Treatments is Premature

In what is becoming a concerning pattern for ICER, this study assessing the value of siponimod was conducted far too early and consequently is based on insufficient and limited data. There are no studies comparing siponimod to currently-available MS disease-modifying therapies (DMTs) or showing long-term outcomes. Due to this limited evidence, the study focuses on a small subset of patient outcomes, completely disregarding patient preference and outcomes that matter to patients. The Consortium of Multiple Sclerosis Centers cites this as a main concern in their comment letter saying, "The decision to focus the review on siponimod appears biased and premature."

The Study Fails to Capture Patient and Caregiver Preference

ICER's assessment fails to appropriately capture MS patient preferences, ignoring the voice and needs of those who are most directly impacted by this disabling disease. Instead of attempting to remedy this gap through patient engagement, ICER's strict timeline and inflexible methods for collecting stakeholder input place additional barriers in front of patient advocates. In their comment letter to ICER, the MS Coalition urged "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." Failing to do so means important outcomes that matter to patients and their familiars will continue to be ignored. The MS Coalition focuses on this in their comment letter to ICER offering to partner with them on patient engagement endeavors and saying "it is critical that the review reflect the real life experiences, perspectives, hopes and concerns of people living with MS."

The Study Relies on Outdated and Faulty Data

In evaluating mortality rates for Expanded Disability Status Scale (EDSS) stages, ICER selected a study from 1997² over a similar study published in 2018.³ Whereas the sensitivity analysis of the economic evaluation uses the more recent and more accurate source mortality data, the model ICER uses to develop their value-based price recommendation was based on data from the 1997 study. Similarly, ICER chose to utilize data on health state utility published in a 2007 study rather than a comparable study published in 2016 because they "have been cited extensively in previous economic models." The choice of an older source because it has been cited more extensively indicates strong selection bias. It is obvious that a study published 12

² Pokorski RJ. Long-term survival experience of patients with multiple sclerosis. JOURNAL OF INSURANCE MEDICINE-NEW YORK-. 1997 Jan;29:101-6.

³ Harding K, Anderson V, Williams O, Willis M, Butterworth S, Tallantyre E, Joseph F, Wardle M, Pickersgill T, Robertson N. A contemporary study of mortality in the multiple sclerosis population of south east Wales. Multiple sclerosis and related disorders. 2018 Oct 1;25:186-91.

years ago would be more frequently cited than one from 2 years ago. Equally obvious is that fact that more recent publications are likely to have more relevant data.

Conclusion

ICER has once again missed the mark by showing callous disregard for patients. Instead of working to engage with MS patients and taking their preferences and needs into consideration in evaluating a treatment designed for MS patients, ICER instead has chosen to rely on dated studies and mechanisms that are widely considered flawed. We encourage ICER to take a hard look at the tools and timing of its reviews, and prioritize accurate data and patient engagement over speed of reviews. The National Multiple Sclerosis Society's assertion that a review at this time is inappropriate based on the new FDA approvals is a clear example of the risk inherent in ICER's rush to judgment on value. We especially and strongly oppose the use of negative utilities that would suggest patients with MS experience a state worse than death. We urge ICER to heed the Society's call to discontinue the current review.

Sincerely,



Tony Coelho
Chairman, Partnership to Improve Patient Care



April 3, 2019

Steven D. Pearson, MD, MSc, FRCP
President
Institute for Clinical and Economic Review
One State Street, Suite 1050
Boston, MA 02109 USA

RE: Siponimod for the Treatment of Secondary Progressive Multiple Sclerosis: Effectiveness and Value: Draft Evidence Report

Dear Dr. Pearson:

Patients Rising Now advocates on behalf of patients with life-threatening conditions and chronic diseases for them to have access to vital therapies and services. Access is a matter of survival and quality of life for those patients, and it spans affordability, insurance coverage, and physical access. To support improved access, we are committed to engaging all stakeholders to foster realistic, patient-centered, solution-oriented discussions for particular conditions and the entire U.S. health care system. That is, our goal is a balanced dialogue that illuminates the truth about health care in a just and equitable way.

We appreciate the opportunity to provide our comments on ICER's March 14th Draft Evidence Report about "Siponimod for the Treatment of Secondary Progressive Multiple Sclerosis."

Patient-Center Perspectives

We want to congratulate ICER for working prospectively with the MS Coalition on the survey of MS patients to help illuminate patient specific perspectives and concerns. Doing this is a great step forward for ICER, and is particularly important because of the lack of patient reported information in the single clinical trial for the compound of interest for this draft report, which specifically noted "The EXPAND trial did not evaluate many patient-reported outcomes, and quality of life measurements were conspicuously absent from the results."ⁱ

However, we do want to note that the survey respondents were overwhelmingly white,ⁱⁱ and recent data has shown that the incidence of MS in blacks is not lower than whites, as had previously been believed, but may actually be greater, and further they may have different patterns of manifestation and progression.ⁱⁱⁱ We want to raise this issue because demographic differences may lead to different patient-centered concerns and perspectives about insurance coverage, access, and affordability, as well as quality of life parameters. For example, for U.S. adults 19 to 64 years old, blacks are much more likely to be uninsured compared to whites (14% v. 8%).^{iv} The importance of insurance coverage for patients receiving appropriate treatments is well known, and the draft report also notes that even people insurance can face barriers to accessing treatments: "Clinicians are sometimes hesitant to label a patient as 'progressive' given that doing so may eliminate insurance coverage for certain medications."^v

As you know, MS is now a long-term progressive condition. That is, with currently available treatments, people with MS can expect a relatively long life compared to people with other neurodegenerative diseases such as ALS or Alzheimer's. This means that people with MS have a greater opportunity to benefit from newer treatments that may be developed in their lifetime after they have been diagnosed. This value of hope is an important consideration for evaluating new treatments that may have incremental benefits in slowing progression of diseases such as MS where the expectation for future treatments may be categorized as slowing disease progression, stopping disease progression, and reversing disease progression.

Another patient perspective issue is how an oral treatment affects access, particularly when the other treatment options are infusions or injections that require going to a doctor's office or clinic. Specifically, for people with MS who have mobility problems or problems getting assistance with transport, oral forms may be a more feasible and realistic treatment option. And for people with MS who are working, not having to go to get infusion twice year also would likely mean not having to miss two days of work. And oral treatment options also reduce disutility for caregivers by reducing transportation support and time obligations. In addition, different coverage rules (such as step-therapy requirements), and cost-sharing structures between pharmacy and medical benefits (i.e., between treatment with a pill versus an infusion), can create an uneven decision playing field for patients and clinicians as they try to choose between different treatment options. Those economic and coverage rule barriers can interfere with pure clinically based shared patient-clinician decision making. We recognize that the draft report notes some of these differences in its discussion of Coverage Policies^{vi} but it would be better if ICER also explored the variability for coverage differences – particularly between private insurance plans and Medicare.

We would hope that these patient perspectives and factors would be extensively discussed at ICER's May 23rd meeting about this topic, and presented in depth in the final report.

Methodology

We are encouraged that in this draft report ICER did not attempt to extrapolate data from non-comparable trials and populations. Doing so could provide quantitative results that would be meaningless and thus misleading, i.e., the results could be statistically significant, but clinically irrelevant. Thus, analyzing the single trial's results that compare siponimod to best supportive care is the responsible and ethical choice.

Budget Impact

As we've noted in the past, ICER's budget impact threshold process and calculations are somewhat arbitrary, and can be anti-patient and anti-innovation. For example, increasing the number of FDA approvals results in lower threshold number. Specifically, since the FDA approved 59 new drugs in 2018, using a two-year average for new drug approvals, the threshold would be \$640 million rather than ICER's current threshold of \$991 million (derived from 2016 and 2017 approval data). And a three-year average (2016-2018), would result in a \$794 million threshold. Further, ICER's budget threshold formula implicitly assumes that all new drugs are additive to health care costs. This assertion conflicts with the Congressional Budget Office's finding that for Medicare, every 10% increase in usage of prescription drugs by Medicare enrollees is expected to produce 2% reduction in spending on medical services.^{vii}

Technical Issue:

- In Tables 4.4. and 4.5 (on pages 45 and 46 of the draft report), is the label for the top row supposed to be “EDSS at the Start of the Next (or Following) Year,” or “EDSS at End of the Year” rather than “EDSS at Start of the Year”? We are a bit confused since the tables in the draft report have the same label on both axes.
- In the Cost Effectiveness analysis, was the current situation of 22% of people with SPSS using ocrelizumab off-label^{viii} considered? That is, was it assumed that the same percentage of people with SPSS would continue to receive ocrelizumab, or would that percentage decrease with those taking siponimod? And if there was a substitution of siponimod for ocrelizumab, were any savings from the reduction in the use of ocrelizumab considered, or was it assumed that “best supportive care” did not include any use of ocrelizumab?
- The lead author for the draft report (Dr. Ravi Sharaf) does not appear to have any expertise in neurology or autoimmune conditions, and this appears to be his first work for ICER. We are somewhat concerned about his lack of experiences and would hope ICER would engage more focused experts in the future.

Conclusions & Recommendations

Patients Rising Now continues to follow ICER’s activities and publications, and encourages ICER to continue to expand how it incorporates patient-centered and real-world evidence into its work. We believe that ethical choices should not primarily rely on economic analyses that erect barriers to patients accessing FDA approved treatments – which we believe would contribute to more adverse outcomes for patients and diminishes the very real value of hope delivered by new treatment options. One way to ensure that does not happen is for all stakeholders – government, regulators, payers, companies, analysts, health technology assessment organizations – to be as transparent as possible about their data and analytical methodologies for making access, coverage, and payment decisions. Specifically, we encourage transparency about projections and modeling because outputs and conclusions from those processes are only as valid as the certainty of the data and the assumptions they are based upon.

Patients Rising Now is encouraged that ICER’s draft report on siponimod and SPMS is more patient focused than many other of ICER’s reports, and hope that this is the beginning of a trend for the organization.

Sincerely,



Terry Wilcox
Co-Founder & Executive Director, Patients Rising Now

ⁱ Draft report, “Siponimod for the Treatment of Secondary Progressive Multiple Sclerosis,” p. 37

ⁱⁱ Draft report, “Siponimod for the Treatment of Secondary Progressive Multiple Sclerosis,” p. 11

ⁱⁱⁱ “Incidence of multiple sclerosis in multiple racial and ethnic groups,” *Neurology*. 2013 May 7;80(19):1734-9, and “African Americans: National Multiple Sclerosis Society,” <https://www.nationalmssociety.org/What-is-MS/Who-Gets-MS/African-American-Resources> (Accessed 3/22/19)

^{iv} Kaiser Family Foundation, “Changes in Health Coverage by Race and Ethnicity since Implementation of the ACA, 2013-2017” Figure 5.

^v Draft report, “Siponimod for the Treatment of Secondary Progressive Multiple Sclerosis,” p. 2

^{vi} Draft report, “Siponimod for the Treatment of Secondary Progressive Multiple Sclerosis,” p. 16

^{vii} “Offsetting Effects of Prescription Drug Use on Medicare’s Spending for Medical Services,” Congressional Budget Office, November 2012.

^{viii} Draft report, “Siponimod for the Treatment of Secondary Progressive Multiple Sclerosis,” p. 33