INSTITUTE FOR CLINICAL AND ECONOMIC REVIEW

Siponimod for the Treatment of Secondary Progressive Multiple Sclerosis: Effectiveness and Value

Response to Public Comments on Draft Evidence Report

May 2, 2019

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Manufacturers		
Novartis		
1.	*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% of the approximately 400,000–500,000 MS patients in the United States. 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. 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.	We have reported the range in Section 1: Background.
2.	*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). 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.	The clinical and economic reviews evaluate outcomes associated with the SPMS population as a whole, as well as active and non-active subgroups.
3.	*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. 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	We have chosen to evaluate siponimod in the overall SPMS population in line with the phase III clinical trial as well as a second base case for active SPMS defined by active relapses in the prior two years, given the available data and the FDA approval. We are also evaluating siponimod in non-active SPMS in a scenario analysis. In this way we hope to provide information for key populations of interest.

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	two years). 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. 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.	
4.	*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. 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."	We have chosen to evaluate siponimod versus best supportive care in the base case. For the overall SPMS population we feel this is most appropriate given the lack of evidence for benefit of other therapies. In the active SPMS subgroup our best data are from the randomized trial of siponimod where it was apparently felt to be clinically appropriate to compare with BSC (as reflected by the placebo arm). However, we have also used data from the MAIC provided by Novartis to compare siponimod with beta-interferon in a scenario analysis.
5.	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-confidence suggests that	These data indicate that there is a substantial proportion of the population 25% to 37% that are currently on best supportive care. Our report will also include a comparison against an alternative DMT, but given the data limitations and requisite assumptions this analysis will not be in the base case.

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	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.	
6.	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.	As described above, we intend to use the MAIC analysis in select scenario analyses.
7.	*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. 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. 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.	As described above, we intend to use the MAIC analysis in select scenario analyses.
8.	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	As described above, we intend to use the MAIC analysis in select scenario analyses.

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	methodologically acceptable, most accurate option for addressing differences in study population characteristics.	
9.	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.	As described above, we intend to use the MAIC analysis in select scenario analyses.
10.	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.	Thank you for participating in our model transparency program. We found siponimod to be cost effective (below the threshold of $150,000 per additional QALY) when compared to BSC when the price of the drug is lowered to $995 per month.
11.	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.	Probability of death for each year of life was taken for males and females separately based on 2016 data from the Human Mortality Database. The model and source were cross-checked and found to be correct. Only three decimal points were shown in the Excel model rather than the five decimals shown in the original source. This led to rounding of the number displayed in Excel without changing the inputs or calculations.
12.	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. Given the expectation that relapse rates will vary by EDSS state, Novartis suggests the use of annualize relapse rate per Bozkaya (2017).	We acknowledge the relapse rates are likely to vary by EDSS state and may be different in the real world versus the clinical trial due to the selective nature of the clinical trial population. We will therefore use two sets of relapse rates depending on the population--overall (Pokorski 1997) vs. active (Bozkaya 2017).
Genentech		
1.	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	Thank you.

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	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.	
2.	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). 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. 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.	See below for our modifications.
3.	*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. 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.	We have added 24-week confirmed progression ≥20% for the T25FW and 9HPT to the ocrelizumab data summary.
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.	We have added these results to the ocrelizumab data summary.
Patient Groups		
MS Coalition		
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"	Given the lack of therapies for non-active SPMS, the clinical and cost effectiveness of siponimod in all patients with SPMS remains of interest to multiple stakeholders. Similarly, in the absence of effective therapies for non-active SPMS, we believe best supportive care is a relevant

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	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.	comparator. However, as noted above, we have included a scenario analysis that compares siponimod to interferon beta-1b using data that is more representative of an active SPMS population. ICER has chosen not to publish value-based price benchmarks for siponimod.
2.	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.	We found it extremely helpful to speak with the people living with SPMS who participated in our small group meeting and of course agree that a three-person group is not a representative sample. We were grateful to partner with the MS Coalition to conduct a survey that captured the experiences and preferences of over 3,000 people living with SPMS. Thank you for your partnership in that effort.
3.	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.	We have chosen to evaluate siponimod in the overall SPMS population in line with the phase III clinical trial as well as a second base case for active SPMS defined by active relapses in the prior two years, given the available data and the FDA approval. We are also evaluating siponimod in non-active SPMS in a scenario analysis. In this way we hope to provide information for key populations of interest. Please note that we are not performing cost-benefit analyses.
4.	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	See above for discussion about appropriate comparators, subgroups, and additional analyses. We acknowledged that if clinical practice and reimbursement policies align with the labeled indication, patients will discontinue after transition from active to non active disease. However, it is unclear if this will actually happen in real world practice (note the use of DMTs off label). Further, there are challenges in estimating when this transition is likely to occur. That said, we have included discontinuation related to the transition to non active disease in our subgroup analysis of active disease with the assumption that

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	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.	patients discontinue at EDSS state 7. This is based on the decline in annualized relapse rate observed in EDSS states 7, 8, and 9 (Bozkaya 2017).
5.	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. 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 disfunction, 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	We acknowledge that there are data limitations related to SPMS-specific healthcare costs. However, the model includes EDSS-specific health states and the EDSS states are established as similar for RRMS and SPMS. Although not explicitly included, the factors indicated would be captured in the quality of life and healthcare cost estimates included in the model given the comprehensive nature of the methods underlying these estimates. Further, there are not data to suggest that the cost of relapse would be expected to be higher or lower for SPMS patients versus RRMS patients.
6.	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.	As explained above, we believe the clinical and cost effectiveness of siponimod in all patients with SPMS remains of interest to multiple stakeholders given the dearth of effective therapies for non-active MS.
National MS Society		
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:	Given the lack of therapies for non-active SPMS, the clinical and cost effectiveness of siponimod in all patients with SPMS remains of interest to multiple stakeholders. Similarly, in the absence of effective therapies for non-active SPMS, we believe best supportive care is a relevant comparator. However, as noted above, we have included a scenario analysis that compares

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	• 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 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.	siponimod to interferon beta-1b using data that is more representative of an active SPMS population. ICER has chosen not to publish value-based price benchmarks for siponimod.
2.	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.	We found it extremely helpful to speak with the people living with SPMS who participated in our small group meeting and of course agree that a three-person group is not a representative sample. We were grateful to partner with the MS Coalition to conduct a survey that captured the experiences and preferences of over 3,000 people living with SPMS. Thank you for your partnership in that effort.
3.	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.	We have chosen to evaluate siponimod in the overall SPMS population in line with the phase III clinical trial as well as a second base case for active SPMS defined by active relapses in the prior two years, given the available data and the FDA approval. We are also evaluating siponimod in non-active SPMS in a scenario analysis. In this way we hope to provide information for key populations of interest. Please note that we are not performing cost-benefit analyses.
4.	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.	See above for discussion about appropriate comparators, subgroups, and additional analyses. We acknowledged that if clinical practice and reimbursement policies align with the labeled indication, patients will discontinue after transition from active to non active disease. However, it is unclear if this will actually happen in real world practice (note the use of DMTs off label). Further, there are challenges in estimating when this transition is likely to occur. That said, we have included discontinuation related to the

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	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.	transition to non active disease in our subgroup analysis of active disease with the assumption that patients discontinue at EDSS state 7. This is based on the decline in annualized relapse rate observed in EDSS states 7, 8, and 9 (Bozkaya 2017).
5.	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. 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 disfunction, 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.	We acknowledge that there are data limitations related to SPMS-specific healthcare costs. However, the model includes EDSS-specific health states and the EDSS states are established as similar for RRMS and SPMS. Although not explicitly included, the factors indicated would be captured in the quality of life and healthcare cost estimates included in the model given the comprehensive nature of the methods underlying these estimates. Further, there are not data to suggest that the cost of relapse would be expected to be higher or lower for SPMS patients versus RRMS patients.
6.	*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 QALY is the gold standard for measuring how well a medical treatment improves and lengthens patients' lives, and therefore has served as a fundamental component of cost-effectiveness analyses in the U.S. and around the world for more than 30 years. Because the QALY records the degree to which a treatment improves patients' lives, treatments for people with serious disability or illness have the greatest opportunity to demonstrate more QALYs gained and justify a high price. Moreover, to be responsive to the concerns about the QALY, ICER is working on a plan to more prominently incorporate a calculation of the Equal Value of Life Years Gained (evLYG), which evenly measures any gains in length of life, regardless of the treatment's ability

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		to improve patients' quality of life. More information can be found here: https://icer-review.org/material/the-qaly-rewarding-the-care-that-most-improves-patients-lives/
Partnership to Improve Patient Care		
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.	Given the lack of therapies for non-active SPMS, the clinical and cost effectiveness of siponimod in all patients with SPMS remains of interest to multiple stakeholders. Similarly, in the absence of effective therapies for non-active SPMS, we believe best supportive care is a relevant comparator. However, as noted above, we have included a scenario analysis that compares siponimod to interferon beta-1b using data that is more representative of an active SPMS population. We address concerns about patient and caregiver preferences and chosen data in the comments below.
2.	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.	The health state utilities used in the draft report were derived using methods involving MS patients. The concept of using health states worse than death is grounded in utility theory and has been shown to be valid. However, in response to concerns from patient groups regarding the perception of negative utility states and the availability of alternate valid estimates, we have opted to use the estimates from Harding 2016 in the evidence report.
3.	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."	We recognize that for newly approved treatments there are often limited data available. However, since these medicines are currently available for use by patients, clinicians and payers, reliable information is needed now. This report uses data that are currently available and highlights the limitations of these data as well as the qualitative input of a range of stakeholders.
4.	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	We respectfully disagree that our report did not take patient or caregiver preference into account. ICER partnered with the MS Coalition to conduct a

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	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."	survey that captured the experiences and preferences of over 3,000 people living with SPMS. We also met with a group of patients with SPMS to hear their perspectives first hand. You can find a detailed write-up of the survey in section 1.4 of our report. We have included many direct quotes from patients that reflect their experience, frustrations, and hopes for the future.
5.	In evaluating mortality rates for Expended Disability Status Scale (EDSS) stages, ICER selected a study from 1997 over a similar study published in 2018. 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 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.	In assessing the literature for economic models, we strive to select the most reliable and valid source of inputs for model parameters. In some instances, such as mortality and utility by EDSS state, more than once source is available, with advantages and disadvantages to each set of data. For the base case we chose to present results using established, well-cited datasets within the MS literature. We also acknowledged and presented the new alternative sources of data within the report and tested these inputs in a sensitivity analysis. The results of the scenario did not alter the base case conclusions.
6.	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."	We are delighted to hear that Patients Rising Now appreciated our efforts to highlight the patient perspective in our report.
7.	However, we do want to note that the survey respondents were overwhelmingly white, 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. We want to raise this issue because demographic differences may lead to different patient-centered concerns and perspectives about	Thank you for making these points.

#	Comment	Response/Integration
	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%). 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."	
8.	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 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	Thank you for making these points. We aim to discuss many of these contextual considerations at our public meeting on May 23rd.

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	discussed at ICER's May 23rd meeting about this topic, and presented in depth in the final report.	
Patients Rising Now		
1.	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.	Thank you.
2.	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.	Thank you for this comment. Due to the indication siponimod received, ICER will be removing the budget impact analysis for this report.
3.	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.	Thank you for this comment. The label for the top row of Tables 4.4 and 4.5 should instead be "EDSS at End of the Year." We have updated the report accordingly.
4.	In the Cost Effectiveness analysis, was the current situation of 22% of people with SPSS using ocrelizumab off-label 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?	Ocrelizumab was not included as a comparator in the cost-effectiveness analysis due to a lack of available data. Best supportive care does not include the use of DMTs
5.	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	We use authors who are expert in evidence-based medicine and in systematically reviewing and synthesizing a body of evidence. While expert input and review is vital to our reports, we believe that experts in evidence-based medicine are best

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	of experiences and would hope ICER would engage more focused experts in the future.	able to provide an unbiased look at the therapies we review.