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

Final Evidence Report

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Prepared for

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About ICER

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The findings contained within this report are current as of the date of publication. Readers should be aware that new evidence may emerge following the publication of this report that could potentially influence the results. ICER may revisit its analyses in a formal update to this report in the future.

In the development of this report, ICER's researchers consulted with several clinical experts, patients, manufacturers and other stakeholders. The following clinical experts provided input that helped guide the ICER team as we shaped our scope and report. None of these individuals is responsible for the final contents of this report or should be assumed to support any part of this report, which is solely the work of the ICER team and its affiliated researchers.

For a complete list of stakeholders from whom we requested input, please visit: https://icer-review.org/material/ms-stakeholder-list-2018/.

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List of Abbreviations and Acronyms Used in this Report

9HPT	9-Hole Peg Test
AAN	American Academy of Neurology
AE	Adverse event
ARR	Annualized Relapse Rate
BSC	Best supportive care
BVMT-R	Brief Visuospatial Memory Test Revised
CDP	Confirmed disability progression
CI	Confidence interval
CIS	Clinically isolated syndrome
CMS	Centers for Medicare and Medicaid Services
CNS	Central nervous system
CPT	Current procedural terminology
CYP2C9	Cytochrome P450 2C9
DMT	Disease-modifying therapy
EAN	European Academy of Neurology
ECG	Electrocardiogram
ECTRIMS	European Committee for Treatment and Research in Multiple Sclerosis
EDSS	Expanded Disability Status Scale
EQ-5D	EuroQol five dimensions questionnaire
FDA	Food and Drug Administration
HCPCS	Healthcare Common Procedure Coding System
HR	Hazard ratio
ICER	Incremental cost-effectiveness ratio
JCV	JC Virus
LCD	Local Coverage Determination
MAIC	Matching-adjusted indirect comparison
MS	Multiple sclerosis
MRI	Magnetic resonance imaging
MSFC	Multiple Sclerosis Functional Composite
MSIS-29	Multiple Sclerosis Impact Scale
MSWS-12	12-item Multiple Sclerosis Walking Scale
NCD	National Coverage Determination
NICE	National Institute for Health and Care Excellence
NNT	Number needed to treat
NR	Not reported
OR	Odds ratio
PASAT	Paced Auditory Serial Addition Test
PCE	Personal consumption expenditure
PHC	Personal Health Care
PICOTS	Population, Intervention(s), Comparator(s), Outcome(s), Timing, Setting
PIRA	Progression independent of relapse activity
PML	Progressive multifocal leukoencephalopathy
PPMS	Primary progressive multiple sclerosis
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QALY	Quality-adjusted life year
QoL	Quality of life
RRMS	Relapsing-remitting multiple sclerosis
RR	Rate ratio or risk ratio
S1P	Sphingosine-1-phosphate
SAE	Serious adverse event

SF-12	12-item short form health survey
SPMS	Secondary progressive multiple sclerosis
T25FW	Timed 25-foot walk
SDMT	Symbol Digit Modalities Test
USD	United States Dollars
USPSTF	US Preventive Services Task Force
WAC	Wholesale acquisition cost
WTP	Willingness to pay

Executive Summary

Background

Multiple sclerosis (MS) is a chronic, immune-mediated inflammatory, demyelinating, and neurodegenerative disease of the central nervous system (CNS).[1] Commonly-cited analyses estimate the prevalence of MS in the United States to approximate 400,000 Americans, although a recent analysis suggests the prevalence may be closer to one million.[2-4] MS disproportionately affects women and is typically diagnosed between the ages of 25-45.[5] The onset of symptoms often coincides with an individual's most productive years at home, work, and in the community. Direct medical costs associated with MS management, coupled with indirect costs from lost productivity, have been estimated to total $24.2 billion per year in the United States.[6] As price increases for MS disease-modifying therapies (DMTs) outpace prescription drug inflation, disease-related costs are expected to rise.[6,7]

The diagnostic criteria used to define MS have evolved over time. The clinical course has commonly been characterized as relapsing-remitting or progressive.[8-11] Relapsing-remitting MS (RRMS) is a relapsing phenotype that is the initial presentation of 85% to 90% of MS patients. It is characterized by "relapses" which are discrete clinical episodes of neurologic deficits that usually reflect an inflammatory demyelinating event in the CNS, with or without recovery.[9] Progressive MS comprises primary progressive MS (PPMS) and secondary progressive MS (SPMS). The clinical course in PPMS and SPMS is characterized and distinguished from RRMS by increasing neurologic disability that occurs independent of, or in the absence of, relapses. PPMS involves a progressive course from disease onset. SPMS is a progressive course that develops following an initial relapsing-remitting course.[8,9] RRMS and progressive MS are categorized as "active" or "not active" based on the presence or absence of clinical relapse or inflammatory activity on magnetic resonance imaging (MRI). Studies conducted prior to the advent of MS DMTs showed that most patients with RRMS transitioned to SPMS within 25 years,[12,13] though the risk of conversion may be lower, given early treatment with highly effective DMTs as well as changes in classification with newer imaging modalities that have greater sensitivity to detect CNS inflammation.[14]

Distinguishing between relapsing-remitting and progressive phenotypes can be challenging and the phenotypes can overlap.[8,9] It can be difficult to determine whether a patient has truly transitioned to SPMS (i.e., accumulating disability independent of relapses) versus when they are having incomplete recovery from frequent relapses.

The therapeutic goal in MS is to decrease disease activity and disability progression. The Food and Drug Administration (FDA) has approved more than 10 DMTs for "relapsing forms" of MS, although prior to March 2019, the FDA did not explicitly define what constituted "relapsing forms of MS" and whether active SPMS was included in this group. The only FDA-approved therapies with *explicit*

indications for non-active progressive MS include ocrelizumab for PPMS and mitoxantrone for SPMS, although use of the latter had been limited by significant short and long-term risks.

Siponimod

Siponimod (Mayzent™, Novartis) is a selective sphingosine-1-phosphate (S1P) receptor modulator that prevents egress of lymphocytes from secondary lymph organs and their entry into the central nervous system. Siponimod also crosses the blood brain barrier and may have direct neuroprotective effects in the CNS.[15] Siponimod has been studied for the treatment of SPMS and is similar in activity to fingolimod, which is an S1P receptor modulator that is FDA-approved for relapsing MS. Fingolimod has not been tested in SPMS but failed to demonstrate efficacy in PPMS.[16] Cardiac side effects from S1P receptor modulators can necessitate cardiac monitoring in some patients.

In March 2019, the FDA approved siponimod "for the treatment of relapsing forms of MS, including "clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults."[17] Shortly after that, the FDA stated, "Active SPMS is one of the relapsing forms of MS, and drugs approved for the treatment of relapsing forms of MS can be used to treat active SPMS."[18] This latter statement, in particular, clarified that many therapies currently approved for relapsing forms of MS are approved for active SPMS.

Much of the interest in siponimod, however, has been due to its evaluation in both active and non-active SPMS, where it has primarily been studied. Given the lack of therapies for non-active SPMS, we believe the clinical and cost effectiveness of siponimod in all patients with SPMS remains of interest to multiple stakeholders, although treatment of non-active SPMS is outside the approved indications for siponimod in the US.

Scope of the Assessment

This project assesses both the comparative clinical effectiveness and economic impacts of siponimod for the treatment of both active and non-active secondary progressive multiple sclerosis (SPMS). The comparators of focus were best supportive care, beta interferons (interferon beta-1a and interferon beta-1b), natalizumab, and ocrelizumab.

Insights Gained from Discussions with Patients and Patient Groups

Throughout the development of this draft report, we heard from many patients and patient groups about the physical, emotional, and economic impact of living with SPMS. Three patient groups submitted public comments on our draft scoping document and four patient groups commented on the Draft Evidence Report. We also had discussions with several MS patient advocacy organizations, including the Accelerated Cure Project, the Consortium of MS Centers, the National

Multiple Sclerosis Society, and the Multiple Sclerosis Association of America. We also facilitated a group meeting with three people with SPMS to hear directly from patients living with the disease.

Additionally, the Multiple Sclerosis Coalition conducted an online survey of approximately 3,000 MS patients, in consultation with ICER, to help inform this SPMS report. Full survey questions can be found in Appendix F. The survey data showed that patients with SPMS represent a particularly vulnerable population. Caregiver and patient burden are particularly heavy. There is no standard treatment protocol in SPMS, and current treatment options are insufficient. There was overwhelming interest in new treatments for SPMS. Respondents indicated that the biggest reasons they would discontinue a new treatment were uncertainty about long-term risks and side effects. Another common theme was a lack of access to therapies due to geography (i.e., rural areas where infusion centers are less available) or insurance coverage policies.

Comparative Clinical Effectiveness

Commonly Reported Outcomes

Relapses can be reported as a rate per unit time, such as annualized relapse rate, and assessed as either clinical relapses or by MRI activity. The most common measure of disability is the Expanded Disability Status Scale (EDSS) which ranges from 0 to 10 in 0.5 increments and where 0 represents a normal examination and 10 is death from MS (see Table 1.3). Confirmed Disability Progression (CDP) reflects a sustained worsening on the EDSS scale, confirmed at three months (CDP-3) or six months (CDP-6). Additional functional measures include timed walks, assessments of various components of ambulation, timed measures of upper extremity activities, and measures of cognitive processing speed. MRI is also used to assess loss of brain volume.

Clinical Benefits of Siponimod

Evidence on siponimod was derived from the multinational, double-blind, Phase III EXPAND trial.[19] Siponimod reduced the risk of EDSS progression and decreased inflammatory disease activity, as measured by MRI outcomes and relapses. Significant benefits were not observed for other mobility-related measures, including the timed 25-foot walk test and the 12-point Multiple Sclerosis Walking Scale. Siponimod may have a small benefit on cognitive processing speed; data on MS symptoms, quality of life, mortality, caregiver burden, and health care utilization have not been reported.

A central issue raised by any treatment for SPMS is whether it is functioning by reducing relapses (and thus effective mainly for active disease) or whether it also is able to reduce progression in the absence of relapses (and thus has efficacy in non-active disease).

Subgroups defined by the presence or absence of gadolinium-enhancing lesions and by the presence or absence of relapses in the prior two years (both associated with disease activity) were not statistically significantly different from each other, although in both cases the point estimates for confirmed disability progression (CDP) were more favorable in patients with active disease (HRs 0.64 vs 0.82 and 0.67 vs. 0.87, respectively; see Table 3.4 in full report). Post hoc analyses using three different methods to control for the confounding impact of *on-study* relapses suggested a smaller but relatively consistent risk reduction amongst non-relapsing groups for disability progression with siponimod. However, the FDA further explored the question of whether siponimod delays disability progression independent of relapses by conducting additional analyses in subgroups with non-active disease (e.g., patients who did not relapse in the two years prior to *or during* the study).[20] The FDA concluded that these "analyses support the hypothesis that the delay in 3-month CDP is more clearly related to the anti-inflammatory effect of siponimod (yielding a significant treatment effect on the relapsing or active aspect of the disease) than to an effect on the poorly understood 'degenerative' process felt to [dominate] the pathophysiology of SPMS."[20]

Harms

Four deaths occurred in each treatment group of the EXPAND trial. In the siponimod group, these deaths were due to metastatic gastrointestinal melanoma, septic shock, urosepsis, and suicide; an additional patient with metastatic lung cancer died after withdrawing study consent, although the cause of death was unspecified.[19] Discontinuation of the study drug due to adverse events (AEs) was relatively low in the EXPAND trial and occurred in 8% of the siponimod group and 5% of the placebo group (see Table 3.5 of full report).

Rates of non-fatal serious adverse events were similar between groups (18% and 15% for the siponimod and placebo groups, respectively).[19] No individual serious AE occurred in >1% of either patient group. The most frequently reported AEs were headache, nasopharyngitis, urinary tract infection, falls, and hypertension.

Bradycardia at treatment initiation, hypertension, lymphopenia, and macular edema have been associated with S1P-receptor modulation. These events were relatively uncommon in the EXPAND trial but occurred in proportionally more patients in the siponimod group (see Table 3.5 of full report).

Clinical Benefits of Comparator Therapies

Beta Interferons

Our literature review identified two trials of interferon beta-1b in patients with SPMS. A European trial demonstrated a statistical benefit on CDP whereas a North American trial did not.[21,22] The European trial population was younger, with a shorter disease duration, and more active disease,

suggesting that patients with ongoing relapse activity may be more likely to benefit from interferon beta-1b.[23]

We also identified three trials of interferon beta-1a in SPMS populations (SPECTRIMS, Nordic SPMS, and IMPACT trials), none of which demonstrated an effect of interferon beta-1a on disability progression.[24-26]

Common adverse events associated with beta interferons include injection site reaction, lymphopenia, flu-like symptoms, myalgia, leukopenia, neutropenia, elevated liver enzymes, headache, hypertonia, pain, rash, insomnia, abdominal pain, and asthenia.[27-29]

Natalizumab

We identified a single Phase III RCT (ASCEND) of natalizumab in patients with SPMS (n=889).[30] No treatment effect was observed on the composite endpoint, which consisted of the EDSS, the timed 25-foot walk test, and the nine-hole peg test. However, progression defined by the nine-hole peg test was nominally significant, raising the possibility of a benefit on rate of deterioration in upper-limb function.[30] The prescribing information for natalizumab includes a black box warning for progressive multifocal leukoencephalopathy (PML), a viral brain infection that can lead to severe disability or death, and includes additional warnings for herpes infections, liver toxicity, hypersensitivity reactions (including anaphylaxis), and immunosuppression and infections.[31] Common AEs include headache, fatigue, arthralgia, urinary tract infection, lower respiratory infection, gastroenteritis, vaginitis, depression, extremity pain, abdominal discomfort, diarrhea, and rash.

Ocrelizumab

Results from the MS Coalition survey (described in Section 1.4) suggest that ocrelizumab is currently one of the most-used therapies in SPMS. However, we did not identify any studies of ocrelizumab in patients with a documented diagnosis of SPMS. There have been randomized trials of ocrelizumab in relapsing forms of MS (OPERA-I and OPERA-II) and in PPMS (ORATORIO).[32,33] In OPERA I and OPERA II, ocrelizumab demonstrated a treatment benefit relative to interferon beta-1a with respect to relapse rates, CDP-3 and CDP-6, and MRI-related measures. A post hoc subgroup analysis that pooled data from both OPERA-I and OPERA-II attempted to assess a composite endpoint of CDP in patients who were felt to be at higher likelihood of having SPMS.[34] The results of this analysis suggested that ocrelizumab reduced the risk of CDP-3 and CDP-6 by 40% and 36%, respectively. It is uncertain how representative these results are of what would be seen in a prospectively defined population with SPMS. In the ORATORIO trial in patients with PPMS, ocrelizumab decreased the risk of CDP-3 compared with placebo.

Common side effects associated with ocrelizumab include infusion reactions, upper and lower respiratory tract infections, and skin infections.[35] Ocrelizumab's prescribing information also includes a warning about an increased risk of malignancy.

Collectively, the evidence for ocrelizumab in relapsing and primary progressive MS suggests that ocrelizumab is a well-tolerated therapy that delays progression and decreases disease activity in both populations. Given its effectiveness in relapsing and progressive patients, it seems plausible that ocrelizumab would also benefit an SPMS population. However, differences in trial populations and study designs prevent us from being able to quantify the net health benefit of ocrelizumab in SPMS.

Controversies and Uncertainties

Distinguishing between relapsing-remitting and secondary progressive MS is challenging, as the phenotypes often overlap and the transition from RRMS to SPMS is only evident retrospectively. In clinical practice, uncertainty surrounding the transition from RRMS can result in a delay in SPMS diagnosis of approximately three years.[36] Enrollment in the EXPAND trial of siponimod was predicated on investigator attestation that a patient had at least 6 months of progressive increase in disability in the absence of, or independent of, relapses; these attestations were not collected at several study sites. Clinical experts and the FDA noted that this left open the possibility for misclassification of some patients.[20]

Subgroup analyses suggested larger effects in patients with active disease (i.e., those with recent relapses or gadolinium-enhancing lesions) and suggested smaller or no effects in subgroups defined by older age, longer disease duration, the absence of gadolinium-enhancing lesions, and no recent relapses. A central issue raised by any therapy for SPMS is whether it is able to reduce progression independent of relapses and therefore be an effective treatment for patients with non-active disease. Post hoc analyses from the EXPAND trial applied three different statistical methods to attempt to evaluate the effect of siponimod independent of relapse activity.[37] These analyses suggested that siponimod may have a small effect on neurodegenerative processes. However, when the FDA reviewed these post hoc analyses and conducted a few additional analyses, they concluded that there was insufficient evidence to support the approval of siponimod for the full SPMS population.[20] Further study is required to confirm that siponimod is an effective therapy for patients who no longer have inflammatory disease activity or relapses.

It is not clear why siponimod improved 3-month EDSS progression, which is heavily weighted toward ambulatory dysfunction, but had no effect on the timed 25-foot walk test and the 12-point Multiple Sclerosis Walking Scale. The results of the timed 25-foot walk test have been directionally consistent with the results of EDSS progression in other studies in progressive MS.[16,30,38] It is also uncertain whether the 6% absolute risk reduction conferred by siponimod in confirmed disability progression will translate into changes in clinical outcomes that are meaningful to patients.

Long-term safety data for siponimod are not yet available. New therapies frequently have important side effects discovered after FDA approval.[39] The FDA prescribing information for fingolimod, another sphingosine-1-phosphate receptor modulator that was approved for relapsing MS, includes several warnings for serious adverse effects, which include progressive multifocal leukoencephalopathy (PML), posterior reversible encephalopathy syndrome, liver Injury, malignancies, and a severe increase in disability after discontinuation of fingolimod.[40] The median observation period in the core double blind trial period (21 months) of the EXPAND trial may have been too short to see the full outcome benefit and safety of siponimod compared to placebo. Longer term data from an ongoing seven-year open-label extension of EXPAND may provide further evidence on the efficacy and safety of siponimod.

There is a lack of head-to-head trials between DMTs in SPMS. Ocrelizumab has activity in RRMS and PPMS, and in the absence of better data we had substantial uncertainties about the relative benefits of ocrelizumab and siponimod in SPMS.

Summary and Comment

Using the ICER Evidence Matrix (Figure 3.1), we assigned evidence ratings to siponimod relative to best supportive care in patients with active disease (i.e., ongoing relapse activity, the presence of new or enlarging lesions on MRI, or gadolinium-enhancing lesions on MRI) and non-active secondary progressive multiple sclerosis (Table ES1). The lack of head-to-head data as well as our inability to indirectly compare siponimod to other DMTs through network meta-analysis precluded assessment of the comparative net health benefit of siponimod relative to beta interferons, natalizumab, or ocrelizumab.

Table ES1. ICER Evidence Ratings

Intervention	Comparator	Population	ICER Evidence Rating
Siponimod	Best supportive care	Active SPMS	B+
Siponimod	Best supportive care	Non-active SPMS	I

Siponimod Versus Best Supportive Care in Patients with Active SPMS

Compared to best supportive care (i.e., placebo), siponimod significantly reduced the risk of EDSS-defined disability progression and decreased inflammatory disease activity, as measured by MRI outcomes and relapses in the overall trial population. In subgroup analyses of patients who experienced recent relapses and patients with at least one T1 gadolinium-enhancing lesion at baseline, the reduction in the risk of 3-month confirmed disability progression was at least as good as in the overall population and perhaps better.

Siponimod did not show a significant effect on other outcomes related to progression and ambulation, such as the T25FW and 12-point MS Walking Scale. Exploratory analyses failed to show

a clinically meaningful benefit for siponimod on cognition and memory, and the effects of siponimod on quality of life or other MS symptoms were not reported in the EXPAND trial. Nevertheless, the therapy was well-tolerated and unlikely to adversely affect quality of life.

Although the degree to which siponimod delays progression independent of its effect on relapse activity remains uncertain, it is known that poor recovery from relapses can contribute to disability progression in MS. We have high certainty, therefore, that siponimod provides at least a small net health benefit in patients with active SPMS compared to best supportive care ("B+").

Siponimod Versus Best Supportive Care in Patients with Non-Active SPMS

In the subgroup of patients without relapses in the two years prior to the EXPAND study, the point estimate of benefit with siponimod was lower than in the group as a whole, although the differences were not statistically significant. Relapse incidence is a potential confounder of CDP results. To evaluate whether siponimod affects CDP independent of relapses, EXPAND trial investigators conducted post hoc exploratory analyses to control for the confounding impact of *on-study* relapses. The results, some of which reached statistical significance, suggested a relatively consistent risk reduction for disability progression with siponimod.[37] However, the FDA's review of siponimod revealed that elements of the EXPAND trial's conduct (e.g. failure to collect investigator attestations of SPMS), as well as findings from additional post-hoc analyses of progression, lend additional uncertainty about whether siponimod confers a benefit in non-active SPMS. As such, we find the evidence insufficient to determine siponimod's net benefit compared with best supportive care in patients with non-active SPMS ("I").

Siponimod Versus Comparators

In the absence of head-to-head or indirect treatment comparisons of siponimod versus beta interferons, natalizumab, or ocrelizumab, we have insufficient data ("I") to conclude that the net health benefit of siponimod is superior/inferior to any of these other DMTs in patients with SPMS.

Long-Term Cost Effectiveness

We developed a simulation model to estimate the cost-effectiveness of siponimod for patients initiating treatment for SPMS, modeling two patient populations: the overall siponimod clinical trial population (all patients with SPMS) and the subgroup of patients with active SPMS, i.e., with evidence of relapses in the two years prior to enrollment as a marker of disease activity. This latter population was modeled to match the approved FDA indication for siponimod in SPMS. Neither population matches the overall approved siponimod indication of relapsing MS.

In the overall SPMS population where no prior drugs have consistently demonstrated a reduction in the risk of disability progression, we compared siponimod to best supportive care (BSC). Although patients with active SPMS are likely to be treated with other DMTs, we also compared siponimod to

BSC in the subgroup of patients with active SPMS due to the absence of head-to-head data for this group. We used data from a matching-adjusted indirect comparison (MAIC) submitted by the manufacturer of siponimod for a scenario analysis comparing siponimod to DMT treatment in patients with active SPMS.

We used a Markov Model consisting of nine health states based on EDSS score, and death, with a cycle length of one year. At baseline, patients were distributed across the nine health states according to the baseline distribution in the siponimod clinical trial.[19] Patients then transition between health states each cycle over a lifetime horizon, with a discount rate of 3%. Over time, an SPMS patient's EDSS score may increase or remain the same but was assumed not to decrease. A patient can progress to death or have a relapse from any state. In the active SPMS subgroup analysis, a stopping rule was introduced based on the assumption that patients would use siponimod for the approved use in active disease and discontinue when the disease transitions to non-active SPMS. Discontinuation was assumed to occur when active SPMS patients reached an EDSS score of 7. After treatment discontinuation, the patient follows the natural history/supportive care model.

Utility values for quality of life, costs, mortality, and annualized relapse rates were obtained from published literature and applied to each health state.[41-45] Additionally, relapses for the overall SPMS population and active SPMS subgroup were associated with an annualized utility decrement and cost.[46]

The base-case analysis takes a health system perspective with a focus on direct medical care costs only. In the absence of established payer pricing negotiations for siponimod, all analyses were based on the list price for siponimod ($7,273.97 per package of 30).[47] The indirect costs of MS, including productivity losses and caregiver burden, were considered in a societal perspective scenario analysis. [191919191919]The model was developed in Microsoft Excel.

The model estimated the average amount of time that patients spent in each health state, defined by EDSS category. Model outputs included total costs, life-years, ambulatory life-years (time spent in EDSS state <7), quality-adjusted life years (QALYs), and incremental costs per additional life year, ambulatory life year, and QALY over a lifetime time horizon. Cost effectiveness ratios for the overall SPMS population and subgroup with active SPMS were calculated versus BSC; cost-effectiveness ratios were also calculated versus interferon beta-1b as a scenario analysis using the MAIC analysis. As a net price for siponimod was not available at the time of analysis, list price for siponimod ($7,273.97) was compared against the net price for interferon beta-1b ($4,119.90). Further details on the model structure and assumptions are provided in Section 4 of the full report.

Base-Case Results

Total discounted costs, life-years, ambulatory life-years, and QALYs over the lifetime horizon are shown in Table ES2. Among the overall SPMS population, discounted costs over the projected lifetime were approximately $283,000 for BSC and $1.15 million for siponimod. Discounted life expectancy from start of treatment (age 48 years) was 14.4 years for BSC and 14.6 years for siponimod. Discounted life-years with ambulation from start of treatment was 4.45 years for BSC and 5.16 years for siponimod. Finally, projected discounted QALYs were 2.66 for BSC and 3.41 for siponimod.

Among the subgroup of patients with active SPMS, projected discounted costs, life-years, ambulatory life-years, and QALYs for BSC were approximately $307,000, 14.4 years, 4.45 ambulatory years, and 1.48 QALYs. Results for siponimod were $714,000, 14.7 years, 5.69 ambulatory life-years, and 2.42 QALYs.

Table ES2. Base-Case Results (Discounted)

Regimen	Cost	LYs	Ambulatory LYs	QALYs
Overall SPMS Population				
Siponimod	$1,148,000	14.6	5.16	3.41
BSC	$283,000	14.4	4.45	2.66
Active SPMS Population				
Siponimod	$714,000	14.7	5.69	2.42
BSC	$307,000	14.4	4.45	1.48

LY: life year, QALY: quality-adjusted life year

We also calculated the incremental cost per additional life-year, ambulatory life-year, and QALY for siponimod compared to BSC (Table ES3). When compared to BSC for the overall SPMS population, the cost per additional life-year was $3.76 million, cost per additional ambulatory life-year was $1.22 million, and cost per additional QALY was $1.15 million. Among the subgroup of patients with active SPMS, the cost per additional life-year, ambulatory life-year, and QALY were $1.57 million, $329,000, and $433,000, respectively.

Table ES3. Pairwise Results for Siponimod Compared to BSC

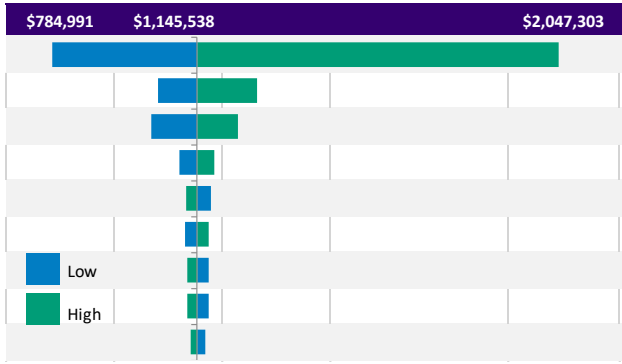
Regimen	Incr. Cost	Incr. LYs	Incr. Ambulatory LYs	Incr. QALYs	Cost/LY	Cost/ Ambulatory LY	Cost/QALY
Overall SPMS Population							
Siponimod	$865,000	0.23	0.71	0.75	$3,760,000	$1,220,000	$1,150,000
Active SPMS Population							
Siponimod	$407,000	0.26	1.24	0.94	$1,570,000	$329,000	$433,000

BSC: best supportive care, ICER: incremental cost-effectiveness ratio, Incr.: incremental, LY: life year, QALY: quality-adjusted life year

Sensitivity Analyses

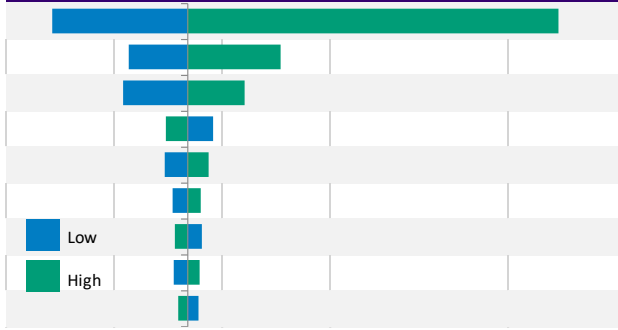
To demonstrate effects of uncertainty on both costs and health outcomes, we varied input parameters across plausible ranges to evaluate changes in the cost per additional QALY for siponimod compared to BSC. Uncertainty in the hazard ratio for confirmed disability progression, relapse risk ratio, and cost of siponimod had the largest impact on model results for the overall SMPS population and for the subgroup with active SPMS (Figure ES1, Figure ES2). The results of the probabilistic sensitivity analysis can be found in Section 4 of the full report. Based on 5,000 model iterations, no iterations (0%) had an additional cost-per-QALY result below the threshold of $150,000 per QALY gained for the overall SPMS population or subgroup with active SPMS (Figure ES3).

Figure ES1. One-Way Sensitivity Analysis for the Overall SPMS Population



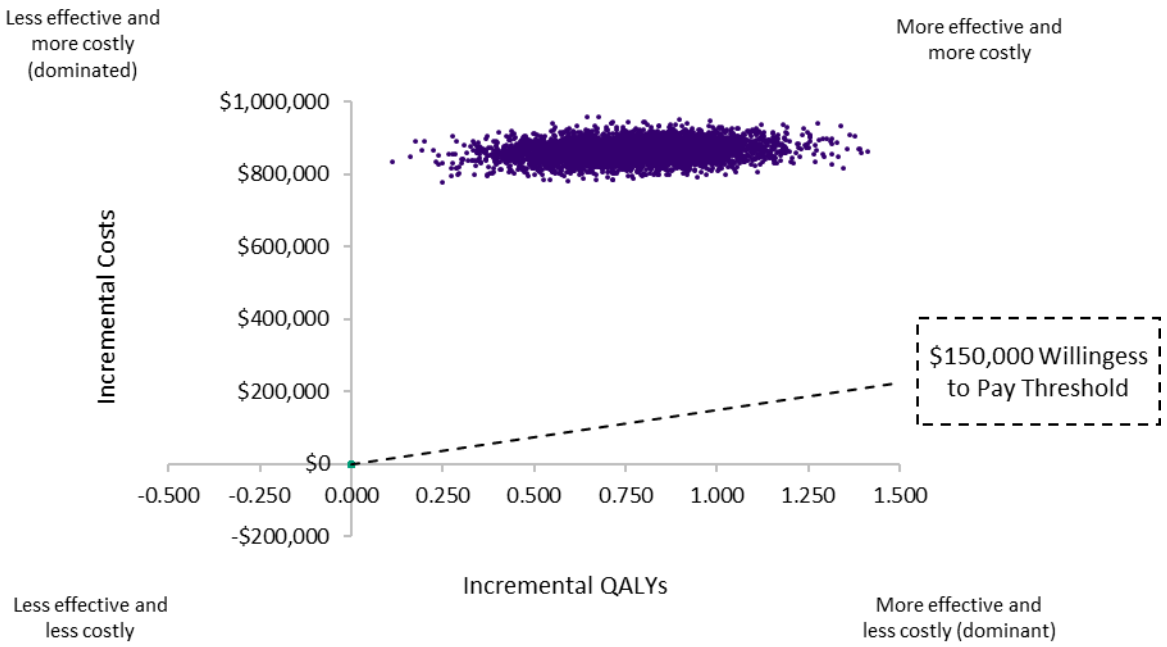
Parameter	Base case	Low Value	High Value	Low Result	High Result	Δ
HR of progression for siponimod	0.79	0.65	0.95	$784,991	$2,047,303	$1,262,312
Relapse RR for siponimod	0.450	0.340	0.590	$1,049,555	$1,295,825	$246,270
Siponimod list price per 30 days	$7,274	$6,547	$8,001	$1,030,066	$1,248,307	$218,240
Proportion of relapses which are mild/moderate	70.8%	63.7%	77.9%	$1,101,509	$1,187,794	$86,285
Utility for EDSS 6	0.481	0.433	0.529	$1,179,342	$1,117,042	$62,301
Discount rate for outcomes	3.0%	2.7%	3.3%	$1,114,697	$1,173,279	$58,582
Discount rate for costs	3.0%	2.7%	3.3%	$1,174,913	$1,120,473	$54,440
Annual utility decrement of severe relapse	0.302	0.272	0.332	$1,173,221	$1,121,977	$51,244
Annual utility decrement of mild/moderate relapse	0.091	0.082	0.100	$1,165,632	$1,128,228	$37,404

Figure ES2. One-Way Sensitivity Analysis for the Active SPMS Subpopulation



Parameter	Base case	Low Value	High Value	Low Result	High Result	Δ
HR of progression for siponimod	0.67	0.49	0.91	$339,727	$688,697	$348,970
Relapse RR for siponimod	0.45	0.34	0.59	$392,318	$497,069	$104,751
Siponimod list price per 30 days	$7,274	$6,547	$8,001	$388,410	$472,058	$83,649
Utility for EDSS 6	0.481	0.433	0.529	$450,570	$417,892	$32,678
Proportion of relapses which are mild/moderate	70.8%	63.7%	77.9%	$417,012	$447,626	$30,613
Mean age at baseline (years)	48.0	43.2	52.8	$422,337	$442,241	$19,904
Annual utility decrement of severe relapse	0.302	0.272	0.332	$442,475	$424,300	$18,175
Discount rate for outcomes	3.0%	2.7%	3.3%	$423,308	$441,045	$17,737
Annual relapse rate for EDSS 6	1.100	0.990	1.210	$440,174	$426,192	$13,982

Figure ES3. Probabilistic Sensitivity Analysis: Incremental Cost-Effectiveness Plane for Cost per Additional QALY for Siponimod Compared to BSC for Overall SPMS Population



BSC: best supportive care, QALY: quality-adjusted life year, SPMS: secondary progressive multiple sclerosis, WTP: willingness-to-pay.

Multiple scenarios were explored, varying sources of inputs and key assumptions of the model. Some alternative scenarios resulted in lower costs and improved outcomes compared to the base case. However, incremental cost per QALY remained well above $150,000 per life year, per life year of ambulation, and per QALY. Results of the MAIC scenario comparing siponimod to the European trial of interferon beta-1b, a trial with a relatively high proportion (approximately 70%) of patients with active SPMS, were $4.83 million per life-year gained, $1.37 million per ambulatory life-year gained, and $2.11 million per QALY gained for siponimod compared to interferon beta-1b. These represent conservative estimates, as contractual discounts on the list price for siponimod would result in more favorable cost-effectiveness results for siponimod vs interferon beta-1b. A discount of approximately 31% off the list price of siponimod would be required to meet the $150,000/QALY threshold versus interferon beta-1b in this scenario.

Threshold Analyses

Prices for each drug that would achieve cost-effectiveness thresholds ranging from $50,000 to $150,000 per QALY gained are presented in Table ES4.

Table ES4. Annual Costs of Siponimod to Reach Cost per QALY

Drug	Base-Case Cost	$50,000/QALY	$100,000/QALY	$150,000/QALY
Overall SPMS Population				
Siponimod	$88,561	$4,529	$8,364	$12,199
Active SPMS Population				
Siponimod	$88,561	$11,980	$21,988	$31,996

QALY: quality-adjusted life year

Model Validation

Model validation followed standard practices in the field. We tested all mathematical functions in the model to ensure they were consistent with the report. We also conducted sensitivity analyses with extreme input values to ensure the model was producing findings consistent with expectations. Further, independent modelers tested the mathematical functions in the model as well as the specific inputs and corresponding outputs. Finally, we shared the model with stakeholder manufacturers to collect feedback on both the approach and construction of the model.

Model validation was also conducted in terms of comparisons to other model findings. We searched the literature to identify models that were similar to our analysis, with comparable populations, settings, perspective, and treatments.

Summary and Comment

For both the overall SPMS population and subgroup with active SPMS, costs per additional QALY gained with siponimod versus BSC were estimated to exceed the commonly-cited threshold of $150,000 per QALY. Results of the base case were $1.15 million per QALY for the overall SPMS population and $433,000 per QALY for the subgroup with active SPMS.

There are a number of limitations to the model due to inadequate data for comparators studied in SPMS and for SPMS as a disease state. For example, annual relapse rates for those with active SPMS by EDSS health state are unknown. It is also unknown if the cost or disutility for a relapse in SPMS differs from that of a relapse in RRMS. Best estimates and assumptions were used within the model and were tested under a variety of assumptions and alternative sources of model inputs, none of which drove the incremental cost per QALY below the threshold of $150,000 per QALY gained with siponimod.

Potential Other Benefits and Contextual Considerations

Our reviews seek to provide information on potential other benefits offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that would not have been considered as part of the evidence on comparative clinical effectiveness. These elements are listed in the table below.

Potential Other Benefits

Table ES5. Potential Other Benefits

Other Benefits	Description
This intervention offers reduced complexity that will significantly improve patient outcomes.	Siponimod is an oral therapy. If it can be used to treat non-active SPMS the other commonly used therapies require infusions or injections.
This intervention will reduce important health disparities across racial, ethnic, gender, socio-economic, or regional categories.	NA
This intervention will significantly reduce caregiver or broader family burden.	It is possible that delaying progression in a patient will reduce caregiver or broader family burden.
This intervention offers a novel mechanism of action or approach that will allow successful treatment of many patients for whom other available treatments have failed.	NA
This intervention will have a significant impact on improving return to work and/or overall productivity.	It is possible that delaying progression will improve/prolong productivity.
Other important benefits or disadvantages that should have an important role in judgments of the value of this intervention.	NA

Contextual Considerations

Table ES6. Potential Contextual Considerations

Contextual Consideration	Description
This intervention is intended for the care of individuals with a condition of particularly high severity in terms of impact on length of life and/or quality of life.	SPMS is a condition with a severe impact on quality of life.
This intervention is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness.	SPMS is a condition with a high lifetime burden of illness.
This intervention is the first to offer any improvement for patients with this condition.	NA
Compared to "the comparator", there is significant uncertainty about the long-term risk of serious side effects of this intervention.	Long-term safety data for siponimod are not yet available.
Compared to "the comparator", there is significant uncertainty about the magnitude or durability of the long-term benefits of this intervention.	Long-term efficacy data for siponimod are not yet available.
There are additional contextual considerations that should have an important role in judgments of the value of this intervention.	NA

Value-Based Price Benchmark

This report evaluated siponimod as treatment for SPMS. As the FDA-approved indication for siponimod is for relapsing forms of MS, and active SPMS is only a portion of the patients with SPMS and does not include RRMS, we are not providing value-based price benchmarks for siponimod as part of this review. ICER is likely to evaluate siponimod in the future when we re-review therapies for relapsing forms of MS.

Potential Budget Impact

As discussed above with regard to value-based price benchmarks, the FDA-approved indication for siponimod (relapsing forms of MS) is different from the focus of this review (SPMS). As such, we are not providing calculations related to the potential budget impact of siponimod.

Midwest CEPAC Votes

The Midwest CEPAC Panel deliberated on key questions raised by ICER's report at a public meeting on May 23, 2019 in Chicago, IL. The results of these votes are presented below, and additional information on the deliberation surrounding the votes can be found in the full report.

1. In patients with ***active*** SPMS, is the evidence adequate to demonstrate that the net health benefit provided by siponimod is superior to that provided by best supportive care?

Yes: 15 votes	No: 2 votes

2. In patients with ***non-active*** SPMS, is the evidence adequate to demonstrate that the net health benefit provided by siponimod is superior to that provided by best supportive care?

Yes: 0 votes	***No: 17 votes***

3. For patients with SPMS, does siponimod offer one or more of the following potential "other benefits or disadvantages" versus best supportive care not adequately captured in the clinical trial data or base-case cost-effectiveness model results?" (select all that apply)

This intervention will significantly reduce caregiver or broader family burden	6/17
This intervention offers a novel mechanism of action or approach that will allow successful treatment of many patients for whom other available treatments have failed.	0/17
This intervention will have a significant impact on improving patients' ability to return to work and/or their overall productivity.	1/17
There are other important benefits or disadvantages that should have an important role in judgments of the value of this intervention.	4/17

4. For patients with SPMS, are any of the following contextual considerations important in assessing siponimod's long-term value for money versus best supportive care? (select all that apply)

This intervention is intended for the care of individuals with a condition of particularly high severity in terms of impact on length of life and/or quality of life.	12/17

This intervention is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness.	13/17
This intervention is the first to offer any improvement for patients with this condition.	2/17
There is significant uncertainty about the long-term risk of serious side effects of this intervention.	10/17
There is significant uncertainty about the magnitude or durability of the long-term benefits of this intervention.	13/17
There are additional contextual considerations that should have an important role in judgments of the value of this intervention.	5/17

Long-Term Value for Money

As described in ICER's value assessment framework, questions on long-term value for money are subject to a value vote when incremental cost-effectiveness ratios for the interventions of interest are between $50,000 and $175,000 per QALY in the primary "base case" analysis. The base case estimates of the cost per QALY for siponimod exceed the higher end of this range, and therefore the treatment is deemed "low long-term value for money" without a vote unless the CEPAC determines in its discussion that the Evidence Report base case analysis does not adequately reflect the most probable incremental cost-effectiveness ratio for siponimod.

Key Policy Implications

Following its deliberation on the evidence, the Midwest CEPAC Panel engaged in a moderated discussion with a policy roundtable about how best to apply the evidence on esketamine for TRD to policy and practice. The policy roundtable members included two patient advocates, two clinical experts, and two payers. The discussion reflected multiple perspectives and opinions, and therefore, none of the statements below should be taken as a consensus view held by all participants. The top-line policy implications are presented below, and additional information can be found in the full report.

Manufacturers

1. To provide fair value to patients and the health system, the manufacturer should lower the price of siponimod so it aligns with the added value it brings to patients.

Payers

2. Evidence and clinical testimony suggested that siponimod does not have a unique role in therapy for any phenotype of MS, including active SPMS. Given its similarities to fingolimod, siponimod should be considered amongst a group of highly effective disease modifying therapies (DMTs) for relapsing forms of MS, including fingolimod, alemtuzumab, natalizumab, and ocrelizumab.[14,32]
3. Payers should offer preferential formulary status to highly effective DMTs with superior safety profiles for patients early in their disease course (i.e., RRMS). For many patients, the evidence is not adequate to determine which DMT would be superior as a first option; therefore, it is reasonable for payers to consider step therapy as a mechanism to achieve lower costs without harming patients. However, any step therapy program must be administered in a way that does not require patients to re-try drugs they have had an inadequate response to in the past, nor prevent clinicians and patients from seeking rapid exceptions based on transparent, evidence-based criteria.
4. Payers may wish to specifically consider granting preferential formulary status to fingolimod when its generic formulation comes to the market.

Patient Advocacy Organizations

5. Patient organizations should view their longer-term mission in support of patients to include active engagement with manufacturers to demand reasonable value-based pricing of the therapies that patients and their families helped bring to the market.

Specialty Societies

6. Testimony from patients and clinicians suggested that patients may benefit more from treatment that is provided by clinicians who are experts in the diagnosis and management of different forms of MS.
7. Individual clinicians and clinical specialty societies should assume a broad leadership role in advocating for patients by taking four actions: 1) highlight and work to address insurance barriers to appropriate care; 2) be vocal witnesses to the negative effects of excessive prices on patients and families, particularly the underserved; 3) integrate considerations of value into clinical guidelines; and 4) embody a broad model of professionalism that calls upon clinicians to work towards a health system that improves access and provides a sustainable model for future innovation through fair pricing.

Regulators

8. The FDA should encourage the standardization and implementation of outcome measures that are interpretable, sensitive, and relevant to an SPMS patient population.

1. Introduction

1.1 Background

Background

Multiple sclerosis (MS) is a chronic, immune-mediated inflammatory, demyelinating, and neurodegenerative disease of the central nervous system (CNS).[1] Commonly-cited analyses estimate the prevalence of MS in the United States to approximate 400,000 Americans, although a recent analysis suggests the prevalence may be closer to one million.[2-4] MS disproportionately affects women and is typically diagnosed between the ages of 25-45.[5] The onset of symptoms often coincides with an individual's most productive years at home, work, and in the community. Direct medical costs associated with MS management, coupled with indirect costs from lost productivity, have been estimated to total $24.2 billion per year in the United States.[6] As price increases for MS disease-modifying therapies (DMTs) outpace prescription drug inflation, disease-related costs are expected to rise.[6,7]

The diagnostic criteria used to define MS have evolved over time. The clinical course has commonly been characterized as relapsing-remitting or progressive, although there can be overlap between these phenotypes.[8-11] Relapsing-remitting MS (RRMS) is a relapsing phenotype that is the initial presentation of 85% to 90% of MS patients. It is characterized by "relapses" which are discrete clinical episodes of neurologic deficits that usually reflect an inflammatory demyelinating event in the CNS, with or without recovery.[9] RRMS is classified as "active" (vs. "not active") in the presence of clinical relapse or inflammatory activity (i.e., new or enlarging T2 lesions or gadolinium-enhancing lesions) on magnetic resonance imaging (MRI). There is no progression of disability during remission; if full recovery does not occur after a relapse, patients experience a step-wise accumulation of disability.

Progressive MS comprises primary progressive MS (PPMS) and secondary progressive MS (SPMS). The clinical course in PPMS and SPMS is characterized by increasing neurologic disability that occurs independent of, or in the absence of, relapses. PPMS involves a progressive course from disease onset. SPMS is a progressive course that develops following an initial relapsing-remitting course.[8,9] Progressive MS is categorized as "active" or "not active" (as per the criteria mentioned above for RRMS), and "with progression" or "without progression," determined by worsening of disability progression independent of relapses. Patients with progressive MS may experience periods of stability during which their disease does not progress. Studies conducted prior to the advent of MS DMTs showed that most patients with RRMS transitioned to SPMS within 25 years,[12,13] though the risk of conversion may be lower, given early treatment with highly effective DMTs as well as changes in classification with newer imaging modalities that have greater sensitivity to detect CNS inflammation.[14]

Distinguishing between relapsing-remitting and progressive phenotypes can be challenging and as noted above, the phenotypes can overlap. The most recent McDonald criteria for MS diagnosis recommend that the phenotype be periodically re-evaluated based on accumulated information.[8,9] There is no biomarker differentiating the entities and the transition from relapsing-remitting to secondary progressive MS is often only evident retrospectively. Clinicians are sometimes hesitant to label a patient as "progressive" given that doing so may eliminate insurance coverage for certain medications.[36] Further, it can be difficult to distinguish whether a patient has truly transitioned to SPMS (i.e., accumulating disability independent of relapses) versus when they are having incomplete recovery from frequent relapses. These factors complicate both MS disease phenotype classification and diagnosis and muddle reporting of the epidemiology of progressive MS.

The therapeutic goal in MS is to decrease disease activity and disability progression. The Food and Drug Administration (FDA) has approved more than 10 DMTs for relapsing forms of MS, although prior to March 2019, the FDA did not explicitly define what constituted "relapsing forms of MS" and whether active SPMS was included in this group. The only FDA-approved therapies with *explicit* indications for non-active progressive MS include ocrelizumab for PPMS and mitoxantrone for SPMS, although use of the latter had been limited by significant short and long-term risks.

Siponimod

Siponimod (Mayzent™; Novartis) is a selective sphingosine-1-phosphate (S1P) receptor modulator that prevents egress of lymphocytes from secondary lymph organs and their entry into the central nervous system. Siponimod also crosses the blood brain barrier and may have direct neuroprotective effects in the CNS.[15] Siponimod has been studied for the treatment of SPMS and is similar in activity to fingolimod, which is an S1P receptor modulator that is FDA-approved for relapsing MS. Fingolimod has not been tested in SPMS but failed to demonstrate efficacy in PPMS.[16] Cardiac side effects from S1P receptor modulators can necessitate cardiac monitoring in some patients.

In March 2019, the FDA approved siponimod "for the treatment of relapsing forms of MS, including "clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults."[17] Shortly after that, the FDA stated, "Active SPMS is one of the relapsing forms of MS, and drugs approved for the treatment of relapsing forms of MS can be used to treat active SPMS."[18] This latter statement, in particular, clarified that many therapies currently approved for relapsing forms of MS are approved for active SPMS.

Much of the interest in siponimod, however, has been due to its evaluation in both active and non-active SPMS, where it has primarily been studied. Given the lack of therapies for non-active SPMS, we believe the clinical and cost effectiveness of siponimod in all patients with SPMS remains of interest to multiple stakeholders, although treatment of non-active SPMS is outside the approved indications for siponimod in the US.

1.2 Scope of the Assessment

This project assesses both the comparative clinical effectiveness and economic impacts of siponimod for the treatment of both active and non-active secondary progressive multiple sclerosis (SPMS). Evidence was collected from available randomized controlled trials and non-randomized clinical trials. We did not restrict studies according to number of patients or study setting. We supplemented our review of published studies with data from conference proceedings, regulatory documents, information submitted by manufacturers, and other grey literature when the evidence met ICER standards (for more information, see https://icer-review.org/methodology/icers-methods/icer-value-assessment-framework/grey-literature-policy/).

Research Questions

To inform our review of the clinical evidence, we developed the following research questions with input from clinical experts, patients and patient groups:

- In patients with SPMS, what is the comparative efficacy, safety, and effectiveness of siponimod versus beta interferons in terms of disability progression, mobility, quality of life, adverse events, and other key outcomes?
- In patients with SPMS, what is the comparative efficacy, safety, and effectiveness of siponimod versus natalizumab in terms of disability progression, mobility, quality of life, adverse events, and other key outcomes?
- In patients with SPMS, what is the comparative efficacy, safety, and effectiveness of siponimod versus ocrelizumab in terms of disability progression, mobility, quality of life, adverse events, and other key outcomes?
- In patients with SPMS, what is the comparative efficacy, safety, and effectiveness of siponimod versus best supportive care in terms of disability progression, mobility, quality of life, adverse events, and other key outcomes?

PICOTS Criteria

In line with the above research questions, the following specific criteria were defined utilizing PICOTS (Population, Interventions, Comparisons, Outcomes, Timing, and Setting) elements.

Population

The population of focus for this review is adults ages ≥ 18 years with secondary progressive multiple sclerosis. As described above, the absence of clear diagnostic indicators makes it difficult to distinguish relapsing-remitting from progressive phentoypes and determine the point at which RRMS transitions to SPMS. Where data were available, we reported outcomes stratified by the

presence of active (i.e., ongoing relapse activity, the presence of new or enlarging lesions on MRI, or gadolinium-enhancing lesions on MRI) and non-active MS.

Interventions

The intervention of interest for this review is siponimod (Mayzent™; Novartis).

Comparators

Comparators of interest were determined with input from patient organizations, clinicians, and manufacturers. The comparators of focus were best supportive care, beta interferons (interferon beta-1a and interferon beta-1b), natalizumab, and ocrelizumab. These therapies represent select treatment options that have shown some efficacy in SPMS and/or are commonly used in practice, irrespective of whether they have FDA indications specific for SPMS. Information about the included comparator therapies are presented in Table 1.1.

Table 1.1. Comparators of Interest for this Review

Drug & Manufacturer	Indication	Recommended Dose	Route of Administration
Natalizumab (Tysabri®) **Biogen**	Relapsing forms of MS	300 mg every 4 weeks	Intravenous
Ocrelizumab (Ocrevus®) **Genentech**	Relapsing or Primary Progressive forms of MS	Initial dose: 300 mg, followed 2 weeks later by a second 300 mg intravenous infusion Subsequent doses: 600 mg every 6 months	Intravenous
Interferon beta-1a (Avonex®) **Biogen**	Relapsing forms of MS	Starting dose: 7.5 mcg with 7.5 mcg dose increases each week for the next 3 weeks until reach recommended dose of 30 mcg once a week	Intramuscular
Interferon beta-1a (Rebif®) **EMD Serono**	Relapsing forms of MS	Start at 20% of the prescribed dose 3 times per week and increase over a 4-week period to the targeted dose, either 22 mcg or 44 mcg 3 times per week	Subcutaneous
Interferon beta-1b (Betaseron®) **Bayer** **Interferon beta-1b (Extavia®)** **Novartis**	Relapsing forms of MS	Starting dose: 0.0625 mg (0.25 mL) every other day, with dose increases over a 6-week period to the recommended dose of 0.25 mg (1 mL) every other day	Subcutaneous

Best supportive care is defined as any non-DMT intervention that is directed towards managing symptoms (e.g., bowel/bladder dysfunction, spasticity, depression, neuropathic pain, fatigue) rather than treating the underlying disease process. Although mitoxantrone is FDA-approved for SPMS, several stakeholders advised us that this treatment is not commonly used due to toxicity concerns. As such, it was not included in our review.

Outcomes

The outcomes of interest are described in Table 1.2.

Table 1.2. Outcomes and Harms

Outcomes	Harms
Bladder and bowel dysfunction	Adverse events associated with death
Caregiver burden	Serious adverse events
Cognitive function	Adverse events leading to discontinuation
Depression	Cardiac toxicity
Disability progression (e.g., Expanded Disability Status Scale [EDSS] score)	Infections, including progressive multifocal leukoencephalopathy
Fatigue	Other adverse events related to S1P- receptor modulators
Health care utilization	
Health-related quality of life	
Mobility	
Mortality	
MRI outcomes (e.g., brain atrophy)	
Pain	
Productivity	
Relapse	

Timing

Evidence on intervention effectiveness and harms were derived from studies of at least twelve months duration.

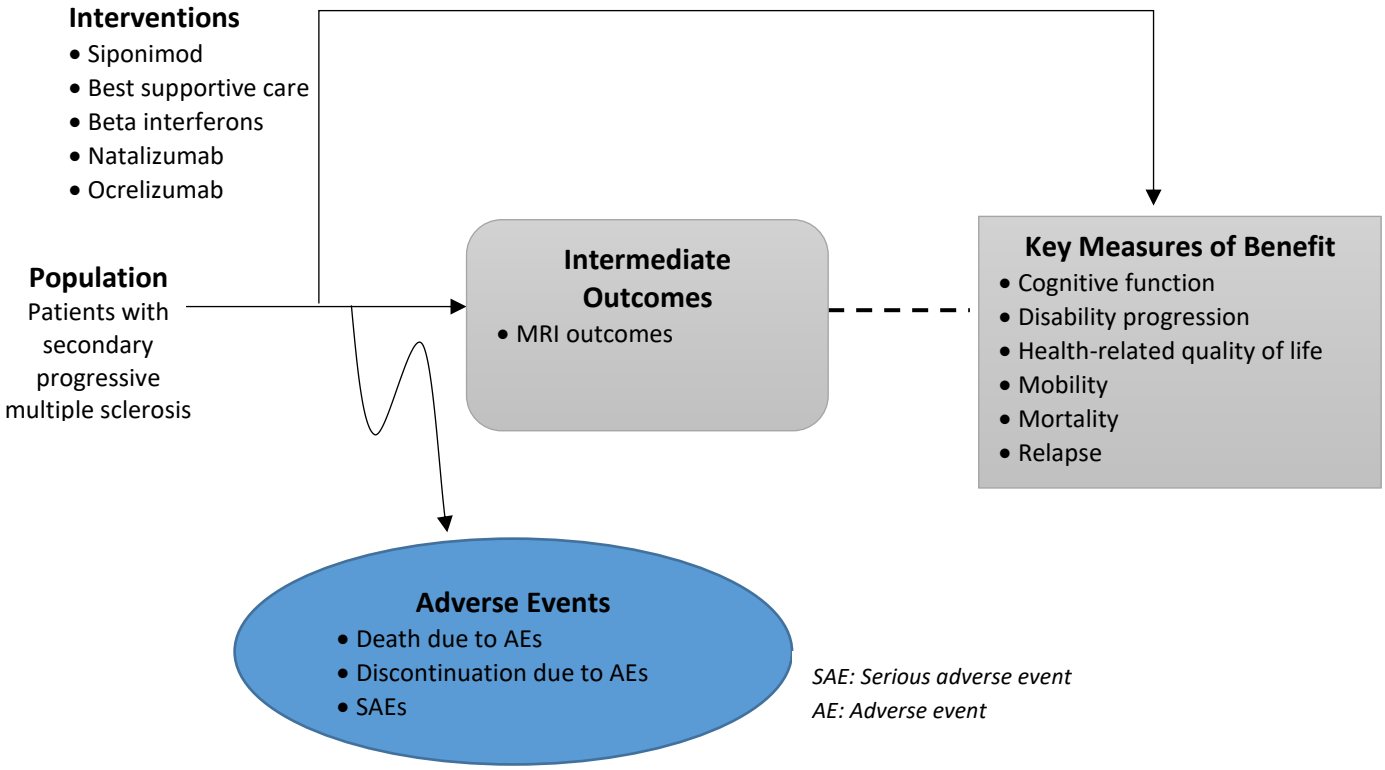
Setting

All relevant settings were considered, including inpatient, clinic, and outpatient settings.

Analytic Framework

The analytic framework for this project is depicted in Figure 1.1.

Figure 1.1. Analytic Framework



The diagram begins with the population of interest on the left. Actions, such as treatment, are depicted with solid arrows which link the population to outcomes. For example, a treatment may be associated with specific health outcomes. Outcomes are listed in the shaded boxes; those within the rounded boxes are intermediate outcomes (e.g., outcomes measured by MRI), and those within the squared-off boxes are key measures of benefit (e.g., disability progression). The key measures of benefit are linked to intermediate outcomes via a dashed line, as the relationship between these two types of outcomes may not always be validated. Curved arrows lead to the adverse events of treatment which are listed within the blue ellipse.[48]

1.3 Definitions

Active MS: MS is defined as active when there is clinical evidence of relapse or inflammatory activity (i.e., new or enlarging lesions or gadolinium-enhancing lesions) detected on MRI.

Relapse: Per the 2017 Revision of the McDonald Criteria, a relapse is "a monophasic clinical episode with patient-reported symptoms and objective findings typical of multiple sclerosis, reflecting a focal or multifocal inflammatory demyelinating event in the CNS, developing acutely or subacutely, with a duration of at least 24 h, with or without recovery, and in the absence of fever or infection. Attack, relapse, exacerbation, and (when it is the first episode) clinically isolated syndrome are synonyms."[9]

Relapsing-Remitting MS (RRMS): MS with periods of partial or complete recovery between acute exacerbations and no significant disability progression between relapses. Eighty-five to ninety percent of MS presents as RRMS at onset.

Primary Progressive Multiple Sclerosis (PPMS): Progressive accumulation of disability from disease onset, usually without relapses. Approximately 10-15% of MS patients are diagnosed with PPMS.

Secondary Progressive Multiple Sclerosis (SPMS): Initial RRMS that is followed by disability progression that occurs in the absence of, or independent of, relapses and/or disease activity.

McDonald Criteria (2010 Revision): Allows the appearance of a new T2 and/or gadolinium-enhancing lesion on MRI at any time following an earlier baseline or reference scan, or the presence of both asymptomatic gadolinium-enhancing and non-enhancing lesions on a presenting patient's first scan for dissemination in time and/or space along with other simplifications.

McDonald Criteria (2017 Revision): The International Panel on Diagnosis of Multiple Sclerosis reviewed the 2010 McDonald criteria and recommended revisions incorporating: 1) the presence of cerebrospinal fluid specific oligoclonal bands in patients with a typical clinically isolated syndrome and clinical or MRI demonstration of dissemination in space, to allow a diagnosis of multiple sclerosis and; 2) the use of symptomatic lesions to demonstrate dissemination in space or time in patients with supratentorial, infratentorial, or spinal cord syndrome and; 3) the use juxtacortical/cortical lesions to demonstrate dissemination in space.[9]

International Advisory Committee on Clinical Trials of MS Revisions (2013): A re-examination of the 1996 phenotype descriptions of MS defined by the US National Multiple Sclerosis Society Advisory Committee on Clinical Trials in Multiple Sclerosis. Activity was defined as clinical relapse and/or MRI activity. Progression was defined as the accumulation of disability measured by at least annual clinical evaluation. Relapsing disease was delineated as: 1) a Clinically isolated syndrome (CIS) that was active or not active, and 2) a Relapsing-remitting disease (RRMS) classified as "not active" or "active." Progressive disease was described as: 1) active with progression, 2) active

without progression, 3) not active but with progression, and 4) not active without progression. Primary progressive (PPMS) was defined as the progressive accumulation of disability from onset and secondary progressive (SPMS) was defined the progressive accumulation of disability after an initial relapsing course.[8]

Outcomes in MS Research

Annualized Relapse Rate (ARR): The per-person average number of relapses in one year for a group of patients. A relapse is usually defined by new or worsening neurologic symptoms that last at least 24-48 hours and that stabilize over days to weeks and resolve gradually, though not always completely.

Confirmed Disability Progression (CDP): Worsening of neurologic deficits, usually defined as an increase on the EDSS scale of 1 point for those with a baseline EDSS ≤ 5.0 or of 0.5 points for those with a baseline EDSS ≥ 5.5, confirmed after a 3- or 6-month period. Six-month CDP is considered a less-sensitive but more robust outcome than 3-month CDP.[19]

Expanded Disability Status Scale (EDSS): The oldest and most commonly used measure of disability in MS. The EDSS ranges from 0 to 10 in increments of 0.5, where 0 is a normal examination and 10 is death from MS (see Table 1.3). A clinician assigns a functional score (FS) to a patient in eight neurologic systems (pyramidal, cerebellar, brainstem, sensory, bladder and bowel, vision, cerebral, other) based on a neurologic examination. Functional System scores range from 0-6 with higher scores indicating greater disability. However, as shown in the table, the overall result is not a simple summation of the functional system scores.

Table 1.3. Expanded Disability Status Scale (EDSS) Grading System*

Grade	Description
0	Normal neurologic examination (all grade 0 in FS, cerebral grade 1 acceptable)
1.0	No disability, minimal signs in one FS (i.e., grade 1 excluding cerebral grade 1)
1.5	No disability, minimal signs in more than 1 FS (more than one grade 1 excluding cerebral grade 1)
2.0	Minimal disability in one FS (one FS grade 2, others 0 or 1)
2.5	Minimal disability in one FS (two FS grade 2, others 0 or 1)
3.0	Moderate disability in one FS (one FS grade 3, others 0 or 1) or mild disability in three or four FS (three/four FS grade 2, others 0 or 1), though fully ambulatory
3.5	Fully ambulatory but with moderate disability in one FS (one grade 3) and one or two FS grade 2, or two FS grade 3, or five FS grade 2 (others 0 or 1)
4.0	Fully ambulatory without aid; self-sufficient; up and about some 12 hours a day despite relatively severe disability, consisting of one FS grade 4 (others 0 or 1) or combinations of lesser grades exceeding limits of previous steps; able to walk approximately 500 meters (m) without aid or resting
4.5	Fully ambulatory without aid; up and about much of the day; able to work a full day; may otherwise have some limitation of full activity or require minimal assistance; characterized by relatively severe disability, usually consisting of one FS grade 4 (others 0 or 1) or combinations of lesser grades exceeding limits of previous steps; able to walk approximately 300 m without aid or rest

Grade	Description
5.0	Ambulatory without aid or rest for approximately 200 m; disability severe enough to impair full daily activities (e.g., to work full day without special provisions; usual FS equivalents are one grade 5 alone, others 0 or 1; or combinations of lesser grades usually exceeding specifications for step 4.0)
5.5	Ambulatory without aid or rest for approximately 100 m; disability severe enough to preclude full daily activities (usual FS equivalents are one grade 5 alone; others 0 or 1; or combinations of lesser grades usually exceeding those for step 4.0)
6.0	Intermittent or unilateral constant assistance (cane, crutch, or brace) required to walk approximately 100 m with or without resting (usual FS equivalents are combinations with more than two FS grade 3+)
6.5	Constant bilateral assistance (canes, crutches, or braces) required to walk approximately 20 m without resting (usual FS equivalents are combinations with more than two FS grade 3+)
7.0	Unable to walk beyond approximately 5 m even with aid; essentially restricted to wheelchair; wheels self in standard wheelchair and transfers alone; up and about approximately 12 hr/day (usual FS equivalents are combinations with more than one FS grade 4+; very rarely, pyramidal grade 5 alone)
7.5	Unable to take more than a few steps; restricted to wheelchair; may need aid in transfer; wheels self but cannot carry on in standard wheelchair a full day; may require motorized wheelchair (usual FS equivalents are combinations with more than one FS grade 4+)
8.0	Essentially restricted to bed or chair or perambulated in wheelchair but may be out of bed itself much of the day, retains many self-care functions; generally, has effective use of arms (usual FS equivalents are combinations, generally grade 4+ in several systems)
8.5	Essentially restricted to bed much of the day; has some effective use of arms; retains some self-care functions (usual FS equivalents are combinations, generally 4+ in several systems)
9.0	Helpless bedridden patient; can communicate and eat (usual FS equivalents are combinations, mostly grade 4+)
9.5	Totally helpless bedridden patient; unable to communicate effectively or eat/swallow (usual FS equivalents are combinations, almost all grade 4+)
10.0	Death due to MS

*Reproduced from Kurtzke, 1983[49]

The EDSS is frequently criticized for being insensitive to small changes, being heavily dependent on mobility, being subjective in some assessments with high intra- and inter-rater variability, and not capturing the full range of patient disabilities. Small changes at higher EDSS scores can mean the difference between ambulation and being wheelchair bound. Additionally, patients at higher baseline EDSS levels may spend more time in those levels than those at lower baseline EDSS levels.[50] This can affect both study entry criteria (which may require progression) and the underlying natural history expected in trials.

Symbol Digit Modalities Test (SDMT): This test examines an individual's cognitive processing speed by presenting the subject with a series of geometric symbols and asking them to use a key to translate the symbols to corresponding single-digit numbers.[51] A change in score of 4 points or 10% is considered clinically meaningful on the SDMT.[52]

The 12-Item MS Walking Scale (MSWS-12): This scale is a patient-reported outcome that measures 12 components of an individual's walking ability. MSWS-12 scores range from 0-100, with higher scores indicating greater levels of walking disability.

The Timed 25-Foot Walk Test (T25FW): This test measures gait velocity by averaging the time it takes a patient to complete two 25-foot walks that are spaced less than five minutes apart. Patients may use assistive devices to complete the walk. A change of 20% or more has been identified as clinically significant.[53]

The Nine-Hole Peg Test (9HPT): This test measures upper arm function by measuring the average time it takes an individual to individually remove nine pegs from a container, place them in corresponding holes in a block, then take each of them out and place them back in the container. The average time it takes an individual to complete four consecutive trials, twice with the dominant hand and twice with the non-dominant hand, makes up the person's score.

Measures Using Magnetic Resonance Imaging (MRI): MRI technology has evolved significantly over the period that MS clinical trials have been performed. Stronger magnets and changing imaging protocols have improved the utility of MRI in the diagnosis and monitoring of patients with MS. However, these improvements lead to challenges in comparing results across studies. The primary outcomes evaluated in MRI studies of MS include:

T1-weighted images:

- Gadolinium-enhancing lesions that are thought to represent areas of active inflammation

T2-weighted images:

- Both the volume and number of T2-weighted lesions as well as the incidence of new and enlarging lesions are frequently reported. The total volume of T2 lesions is used as a surrogate for the total amount of CNS disease, both old and new.

Brain volume:

- In MS, brain volume loss is correlated with the extent of disability, occurs early in the disease course, and continues throughout the disease course.

1.4 Insights Gained from Discussions with Patients and Patient Groups

Throughout the development of this draft report, we heard from many patients and patient groups about the physical, emotional, and economic impact of living with SPMS. We had three patient groups submit public comments on our draft scoping document, one of which was from The Multiple Sclerosis Coalition—a coalition comprised of nine independent organizations focused on improving the quality of life for those affected by MS. We also had discussions with many of these MS patient advocacy organizations, including: The Accelerated Cure Project, The Consortium of MS Centers, The National Multiple Sclerosis Society, and The Multiple Sclerosis Association of America. We also facilitated a group meeting with three people with SPMS to hear directly from patients living with the disease.

These discussions were crucial to providing vivid detail regarding the disease experience and burden of SPMS, and in informing the selected comparators, patient-reported outcomes of interest, and analysis plan for the clinical evidence review and economic model.

Additionally, the Multiple Sclerosis Coalition conducted an online survey of approximately 3,000 MS patients, in consultation with ICER, to help inform this SPMS report. The goal of the survey was to collect information and perspective from patients living with SPMS. Full survey questions can be found in Appendix F. The MS Coalition also plans to publish a separate comprehensive report on the survey results in the coming months. Additional details can be found by contacting the MS Coalition directly through their website at: http://ms-coalition.org.

The results of this survey systematically capture the input and feedback we heard from patients and patient groups. The results are summarized below.

The Multiple Sclerosis Coalition Patient Survey Results

The MS Coalition Survey was conducted throughout January of 2019 and garnered 3,352 responses. Sixty one percent of respondents confirmed they had been diagnosed with SPMS, 13% stated their doctor suspected they were transitioning to SPMS, 11% were unsure if they had an SPMS diagnosis but believed that they did have SPMS, and 15% confirmed they had not received an SPMS diagnosis nor did their doctor suspect they were in transition. Those in this last category were excluded from the survey to ensure an SPMS or possible SPMS population.

The basic demographics of respondents were as follows: 61% had been diagnosed with SPMS within the last ten years, 86% were age 50 or older, 75% identified as female, and 93% as white. Most respondents reported insurance coverage with a commercial carrier or Medicare.

The survey data elucidated the physical, personal, and economic impact SPMS has on patients and their families. Below is a summary of selected results, which corroborated our own conversations with MS patients and advocacy organization leadership.

Patients with SPMS represent a particularly vulnerable population. Those affected are predominantly older and may become disabled, home-bound, or reside in nursing homes. As disability worsens, patients' engagement with health care services, educational resources, and advocacy efforts may diminish. Social isolation increases. Because of the lack of effective therapy in SPMS, respondents perceived that physician engagement with SPMS patients may also decline. There was also a sense that SPMS patients were "second-class citizens" compared to RRMS groups, as advocacy, clinical, and research efforts are often focused on the latter. Depression and resignation were often expressed; mental health was a significant concern.

Patient Comments:

"I've given up thinking that there is anything out there to help me."

"As my MS Specialist said, I have now moved out of the heavily funded RR research category to the little known, least explored category of SPMS.... I may have a rough road ahead."

"I'm willing to try almost anything."

"I lost the ability to stand, transfer, or walk a few steps (with a walker) in 2010, which had a huge impact on my life. My cognitive function has continued to become gradually more impaired. By far the most valuable breakthroughs for me would be treatments/therapies that would address either or both of these challenges."

Caregiver and patient burden are particularly heavy in this population. The day-to-day impact of SPMS symptoms can be devastating. There is often a decrease in or loss of the ability to work for patients (due to physical disability and cognitive challenges) and caregivers (due to caregiver burden) with significant resulting emotional and financial burden. A majority of respondents (59%) reported needing assistance with one or more of the following: personal care, house cleaning, cooking, and transportation. An even larger group (82%), require the use of a mobility aid (e.g. cane/crutches, walker, scooter, wheelchair) every day. Fifty-one percent of respondents indicated they were unable to work due to disability. Among those able to work, 72% reported missing some work in the last year as a result of SPMS symptoms or treatment, with 21% missing eleven or more days. Additionally, 36% reported that their primary caregiver had missed at least one day of work in the last year due to their symptoms or treatment. Many patients commented about needing to leave their jobs because of their SPMS symptoms.

Patient Comments:

"I feel trapped. I was forced to leave my job [on] account [of] the decline in my health. Would desperately like to return to work."

"I used to be a firefighter and I'm no longer able to do the job I love."

"I have had to reduce my on call/overtime hours as I simply don't have the energy."

"I thought I would be working outside the home by now, but my options are really limited. Because of this, our finances are tighter than I thought they'd be. My kids know that I can't do what a lot of other moms can do. My husband has to do so much more because of it."

There is no standard treatment protocol in SPMS, and current treatment options are insufficient. Respondents expressed frustration at the lack of effective treatment directed towards disease progression when it occurs independent of inflammatory activity. The survey listed sixteen available DMTs, some indicated specifically for relapsing or progressive disease, and asked respondents which (if any) of these DMTs they were currently taking. The largest proportion of respondents (37%) reported not being on any of the DMTs listed; 21% of respondents indicated they were currently taking ocrelizumab. Seventy-five percent of survey responders were taking symptom-directed therapies.

There was overwhelming interest in new treatments for SPMS. The majority of respondents indicated they would be very or extremely interested in new treatments that could prevent, stabilize, or improve physical disability, brain atrophy and cognitive decline, and other symptoms (e.g., bowel/bladder).

Respondents indicated that the biggest reasons they would discontinue a new treatment were uncertainty about long-term risks (71%) and side effects (62%). Fifty-four percent of respondents indicated they would discontinue treatment if the treatment is expensive and the same percentage indicated they would stop treatment if their health plan made it difficult to access the drug.

Patient Comments

"In many cases you have to depend on other people. Basic tasks are harder to get done. There is always the struggle between what you want to do and how much energy you have to do it. You live with the fear of the changes that you will face in the future."

"Movement in whatever form is now a continuous problem. Walking in particular. What seemed to be natural is now not. The ability to type and write is slowly getting worse. Going out to see friends & family is very tough. I don't think it is worth it..."

"I feel like the world is passing me by. I can't move as fast or do as much. My senses are fading."

"Now every single thing I do is difficult, which is disheartening. I am determined to continue to solve problems in caring for myself, but realize I may need to move from my own home."

Figure 1.2. SPMS Symptoms and Impact

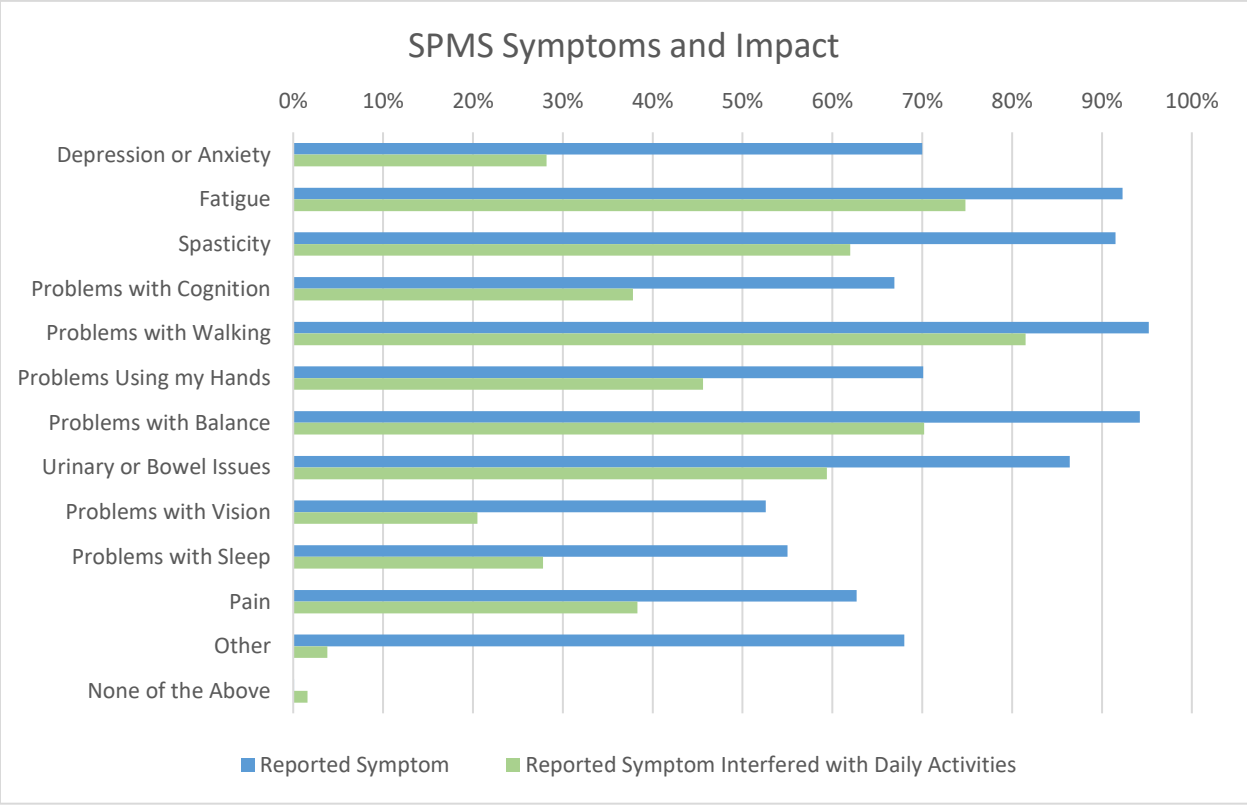


Figure 1.2 details the overwhelming majority of patients who struggle with a wide variety of persistent SPMS symptoms. When asked about the medications they took (other than DMTs) to control these symptoms, 83% of patients indicated that some or all of their symptoms were not well-controlled by these medications.

Another common theme was a lack of access to therapies due to geography (i.e., rural areas where infusion centers are less available) or insurance coverage policies.

ICER thanks the MS Coalition for conducting this survey to support our review.

1.5. Potential Cost-Saving Measures in SPMS

As described in its Final Value Assessment Framework for 2017-2019, ICER now includes in its reports information on wasteful or lower-value services in the same clinical area that could be reduced or eliminated to create headroom in health care budgets for higher-value innovative services (for more information, see https://icer-review.org/final-vaf-2017-2019/). These services are ones that would not be directly affected by siponimod (e.g., reduction in disability or exacerbations), as these services will be captured in the economic model. Rather, we are seeking services used in the current management of MS beyond the potential offsets that arise from a new intervention. During stakeholder engagement and public comment periods, ICER encouraged all stakeholders to suggest services (including treatments and mechanisms of care) currently used for patients with SPMS that could be reduced, eliminated, or made more efficient. No suggestions were received.

2. Summary of Coverage Policies and Clinical Guidelines

2.1 Coverage Policies

To understand the insurance landscape for treatment of SPMS, we reviewed National and Local Coverage Determinations (NCDs and LCDs) from the Centers for Medicare and Medicaid Services (CMS); publicly available coverage policies and formularies for Missouri Medicaid (MO HealthNet), and Illinois Medicaid; Medicare coverage from Cigna (Cigna HealthSpring); and representative national and regional commercial plans (Aetna, Anthem, Cigna, Humana, UnitedHealthcare, and Blue Cross Blue Shield of Kansas City). We surveyed each plan's coverage policies for the comparators reviewed in this report, including natalizumab, ocrelizumab, and five beta interferons: two interferons beta-1a (Avonex and Rebif), peginterferon beta-1a (Plegridy) and two interferons beta-1b (Betaseron and Extavia). Coverage policies for siponimod are not yet available.

We were unable to identify any NCDs or LCDs relating to the use of DMTs for MS.[54] Cigna HealthSpring lists all MS agents at the highest tier (Tier 5), which encompasses specialty drugs and generally incurs a higher cost share for patients than the generic and preferred drug tiers.[55] Most national and regional private payers list natalizumab, ocrelizumab, and the beta interferons on high or specialty formulary tiers. Several payers, including Humana and Blue Cross Blue Shield of Kansas City, cover natalizumab and ocrelizumab, which are both infusion products, under their medical benefits, rather than pharmacy benefits.[56-59]

Of the plans surveyed here, most allow coverage of DMTs for patients diagnosed with SPMS, even though the DMT may be indicated for relapsing forms of MS or PPMS, given that those SPMS patients experience "superimposed relapses." These SPMS patients are generally required to have received a documented diagnosis of a "relapsing form" of MS to receive coverage for DMTs. MO HealthNet is the only public payer surveyed that limits coverage of ocrelizumab, which is indicated for PPMS and relapsing forms of MS, to patients with a documented diagnosis of PPMS.[60] Coverage policies from Cigna, Humana, UHC, and BCBSKC state that these payers may cover ocrelizumab for patients that have been diagnosed with PPMS or relapsing forms of MS.[61-63] Relapsing forms of MS include RRMS and progressive/relapsing MS, which encompasses forms of MS characterized by a continual functional decline and superimposed relapses (e.g., SPMS with relapses, PPMS with relapses).[61] Aetna is the only private payer surveyed that restricts coverage of the interferons and natalizumab to patients with RRMS.[64]

All public and private payers made use of step therapy and prior authorization requirements to manage therapies for MS, and most public payers surveyed list DMTs as non-preferred agents. MO HealthNet and IL Medicaid both list ocrelizumab and natalizumab as non-preferred treatments.[65,66]

Typical step therapy policies require a documented contraindication, intolerance, allergy, or inadequate response to one or more preferred DMTs, as demonstrated by a continuation of or increase in relapses, lesion progression by MRI, or increasing disability as shown by EDSS or neurological examination. For example, patients with an Anthem plan must attempt treatment with one of the preferred interferons (interferon beta-1a [Avonex], interferon beta-1b [Betaseron], or peginterferon beta-1a) before being authorized for treatment with one of the non-preferred interferon agents (interferon beta-1a [Rebif] and interferon beta-1b [Extavia]).[67] Cigna's Performance 3-tier plan specifies that patients must attempt at least one preferred DMT (dimethyl fumarate, fingolimod, glatiramer acetate, interferon beta-1a, interferon beta-1a, peginterferon beta-1a, or teriflunomide) before being approved for natalizumab, and two or more preferred DMTs before attempting ocrelizumab.[68]

Table 2.1. Representative Private Payer Policies for MS Therapies

	Aetna[69]	Anthem[67,70]	Cigna[61,68]	Humana[71]	UHC[62,72]	BCBSKC[59,63]
Interferon beta-1a 30 mcg (Avonex)						
Tier	SP	4	2	SP	2	SP
ST	No	No	No	No	No	No
PA	Yes	Yes	Yes	Yes	Yes	Yes
Preferred Agent	Yes	Yes	Yes	Yes	Yes	Yes
Interferon beta-1a 22/44 mcg (Rebif)						
Tier	SP	NL	2	SP	4	SP
ST	No	Yes	No	No	Yes	No
PA	Yes	Yes	Yes	Yes	Yes	Yes
Preferred Agent	Yes	No	Yes	Yes	No	Yes
Peginterferon beta-1a (Plegridy)						
Tier	SP	4	2	SP	3	SP
ST	No	No	No	No	No	No
PA	Yes	Yes	Yes	Yes	Yes	Yes
Preferred Agent	Yes	Yes	Yes	Yes	Yes	Yes
Interferon beta-1b 0.3 mg (Betaseron)						
Tier	SP	4	2	SP	2	SP
ST	No	No	No	No	No	No
PA	Yes	Yes	Yes	Yes	Yes	Yes
Preferred Agent	Yes	Yes	Yes	Yes	Yes	Yes
Interferon beta-1b 0.3 mg (Extavia)						
Tier	SP	NL	2	SP	N/C	SP
ST	Yes	Yes	No	No	Yes	Yes
PA	Yes	Yes	Yes	Yes	Yes	Yes
Preferred Agent	No	No	Yes	Yes	No	No
Natalizumab (Tysabri)						
Tier	SP	5	3	N/A	-	N/A
ST	Yes	Yes	Yes	Yes	-	Yes
PA	Yes	Yes	Yes	Yes	-	Yes
Preferred Agent	No	No	No	No	-	No

	Aetna[69]	Anthem[67,70]	Cigna[61,68]	Humana[71]	UHC[62,72]	BCBSKC[59,63]
Ocrelizumab (Ocrevus)						
Tier	SP	N/C	3	N/A	N/A	N/A
ST	-	N/A	Yes	Yes	Yes	Yes
PA	Yes	N/A	Yes	Yes	Yes	Yes
Preferred Agent	No	N/A	No	No	No	No

BCBSKC: Blue Cross Blue Shield of Kansas City, N/A: not applicable, N/C: not covered, NL: not listed, PA: prior authorization, SP: specialty, ST: step therapy, UHC: UnitedHealthcare, - : information unavailable

2.2 Clinical Guidelines

Below is a summary of clinical guidelines for the treatment and monitoring of SPMS from the American Academy of Neurology (AAN); European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) and European Academy of Neurology (EAN); MS Coalition; and National Institute for Health and Care Excellence (NICE).

American Academy of Neurology (AAN), 2018[73]

AAN guidelines do not contain treatment sequencing recommendations, but rather recommend that choice of DMT be guided by shared decision-making between the patient and physician. Together, the patient and physician must consider safety, efficacy, tolerability, method of administration, compatibility with patient lifestyle, and cost when selecting a therapy. Physicians are advised to consider starting DMT treatment after one demyelinating event and if two or more brain lesions consistent with MS are detected by imaging. Clinicians may also start DMT treatment for patients with relapsing forms of MS, including SPMS with superimposed relapses, who have had recent clinical relapses or MRI activity. Patients with clinically isolated syndrome (CIS) or relapsing forms of MS who have not had a relapse in the previous two years or recent MRI activity may be monitored closely for disease progression and may ultimately start treatment should their condition worsen. Clinicians should consider switching therapies when a patient experiences at least one relapse, two or more new MRI lesions, or increased disability over a one-year period while on their current DMT. Patients with SPMS who do not experience ongoing relapses, or have MRI activity and have been non-ambulatory for at least two years, may be advised to discontinue treatment with DMTs.

The guidelines recommend that mitoxantrone, an agent that was excluded from our report, not be used in MS in most cases due to the high risk of adverse events. Individuals with highly-active disease should be treated with alemtuzumab, fingolimod, or natalizumab, though the guidelines note that definitions of highly-active disease vary. Patients taking natalizumab have an estimated risk of about 4 per 1,000 of developing progressive multifocal leukoencephalopathy (PML), and this risk is higher for patients with a positive JC virus (JCV) antibody blood test. Clinicians should advise patients about the risk for PML associated with natalizumab and should discuss switching from natalizumab to an agent with lower PML risk for patients who are JCV positive. Patients who discontinue treatment with natalizumab are at increased risk for rebound disease activity (i.e., relapses and MRI activity), and if the subsequent DMT is fingolimod, treatment should begin within eight to 12 weeks to reduce said risk. Given substantial uncertainty regarding the risks of treatment cessation, physicians should advise patients that close follow-up is needed after discontinuation of DMT treatment. Clinicians should recommend that patients who achieve disease stability be allowed to continue therapy with their current agent.

European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) and European Academy of Neurology (EAN), 2018[38]

ECTRIMS and EAN issued joint guidelines on the treatment of MS, which they revise every five years. The guidelines state that clinicians should discuss the uncertain efficacy and safety and tolerability profiles of interferon beta-1a and interferon beta-1b before starting treatment, but these treatments may be used for patients with SPMS. Unlike the AAN guidelines, the ECTRIMS/EAN guidelines also state that mitoxantrone may be used to treat SPMS, after clinicians discuss its risks and benefits and come to a joint decision with their patients. Ocrelizumab may also be used to treat patients with PPMS or SPMS.

All patients who are being treated with DMTs should be monitored regularly by MRI for onset of PML. Patients at high risk for PML (i.e., those who are positive for JCV or have been treated with natalizumab for 18 months or more), should receive an MRI every three to six months. Patients treated with beta interferons or glatiramer acetate who have continued disease activity, as indicated by new or enlarging T2 lesions, should be considered for treatment with a more efficacious drug. Clinicians should take into account the possibility of relapse when considering discontinuation of a treatment, especially natalizumab. The guidelines recommend starting treatment with a highly efficacious drug immediately after stopping another treatment.

MS Coalition, 2018[74]

The MS Coalition consensus guidelines recommend DMT treatment for patients with progressive forms of MS, including SPMS, who experience clinical relapses or inflammatory activity. The coalition also recommends that DMT treatment be started as soon as possible after a diagnosis of relapsing MS or PPMS. Treatment should be continued indefinitely unless response to therapy is inadequate, side-effects become intolerable, patients are unable to adhere to the treatment regimen, or a more appropriate therapy becomes available. Any decision to switch therapies should be driven by shared decision-making between the clinician and patient and should only be considered for medically-appropriate reasons. Clinicians should consider treatment switches when a patient experiences sub-optimal treatment response to their current agent (i.e., relapse, MRI activity, or other clinical activity). Clinicians should consider alternative regimens using a different mechanism of action when changing therapy.

The MS Coalition recommends that clinicians have access to the full armamentarium of MS treatment options given wide variation in mechanism of action, possible contraindications to one or more agents, differing DMT safety profiles, and individual patient preference. Access to treatment should not be dictated by relapse frequency, extent of disability, or patient demographic characteristics. The absence of relapse activity should not be used as justification for treatment cessation.

3. Comparative Clinical Effectiveness

3.1 Overview

To inform our analysis of the comparative clinical effectiveness of siponimod in the treatment of secondary progressive multiple sclerosis, we abstracted evidence from available clinical studies. As mentioned in Section 1.2, comparators of interest included best supportive care, beta interferons, natalizumab, and ocrelizumab. Our review focused on clinical benefits (i.e., disability progression, disease activity, MS symptom relief, mortality, and quality of life), as well as potential harms (drug-related adverse events).

3.2 Methods

Data Sources and Searches

Procedures for the systematic literature review assessing the evidence on siponimod for SPMS followed established best research methods.[75,76] We conducted the review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[77] The PRISMA guidelines include a checklist of 27 items, which are described further in Appendix Table A1.

We searched MEDLINE and EMBASE for relevant studies. Each search was limited to English-language studies of human subjects and excluded articles indexed as guidelines, letters, editorials, narrative reviews, case reports, or news items. All search strategies were generated utilizing the Population, Intervention, Comparator, and Study Design elements described in Section 1. The proposed search strategies included a combination of indexing terms (MeSH terms in MEDLINE and EMTREE terms in EMBASE), as well as free-text terms.

To supplement the database searches, we performed manual checks of the reference lists of included trials and systematic reviews and invited key stakeholders to share references germane to the scope of this project. We also supplemented our review of published studies with data from conference proceedings, regulatory documents, information submitted by manufacturers, and other grey literature when the evidence met ICER standards (for more information, see http://icer-review.org/methodology/icers-methods/icer-value-assessment-framework/grey-literature-policy/).

Study Selection

Subsequent to the literature search and removal of duplicate citations, references went through two levels of screening at both the abstract and full-text levels. Two reviewers independently screened the titles and abstracts of all publications identified using DistillerSR (Evidence Partners,

Ottawa, Canada); a third reviewer worked with the initial two reviewers to resolve any issues of disagreement through consensus.

Citations accepted during abstract-level screening were reviewed as full text. The review followed the same procedures as the title/abstract screening. Reasons for exclusion were categorized according to the PICOTS elements.

Data Extraction and Quality Assessment

Two reviewers extracted key information from the full set of accepted studies (See Appendix D). Elements included a description of patient populations, sample size, duration of follow-up, study design features (e.g., double-blind), interventions (agent, dosage, dosing frequency, method of administration), results, and quality assessment for each study. Extracted data were reviewed for logic and were validated by a third investigator for additional quality assurance.

We used criteria employed by the US Preventive Services Task Force ([USPSTF] see Appendix D) to assess the quality of clinical trials, using the categories "good," "fair," or "poor."[78]

Assessment of Level of Certainty in Evidence

We used the ICER Evidence Rating Matrix to evaluate the level of certainty in the available evidence of a net health benefit for siponimod relative to each of the comparators of focus (see Section 3.4 and Appendix D).[79]

Assessment of Bias

As part of our quality assessment, we evaluated the evidence base for the presence of potential publication bias. Given the emerging nature of the evidence base for newer treatments, we performed an assessment of publication bias for siponimod using the ClinicalTrials.gov database of trials. We scanned the site to identify studies completed more than two years ago that would have met our inclusion criteria and for which no findings have been published. Any such studies may indicate whether there is bias in the published literature. For this review, we did not find evidence of any study completed more than two years ago that has not subsequently been published.

Data Synthesis and Statistical Analyses

Data on relevant outcomes were summarized in evidence tables (see Appendix Tables D1-D6) and are synthesized in the text below. Due to differences in study design, study eligibility criteria, baseline characteristics of study populations, and outcomes assessment, we did not conduct quantitative direct or indirect analyses of the interventions of interest.

3.3 Results

Study Selection

Our literature search identified 2,468 potentially relevant references (see Appendix Figure A1), of which three references relating to one individual study of siponimod met our inclusion criteria. The primary reasons for study exclusion included study population outside of our scope (e.g., patients with RRMS or a general MS population without outcome stratification by phenotype), interventions not of interest (e.g., natural beta interferons), and study designs or types of publications outside the scope of our review (e.g., preclinical studies).

The included study was the Phase III EXPAND trial of siponimod in patients with an SPMS diagnosis, documented EDSS progression in the two years before the study, and no evidence of relapse in the three months prior to randomization.[19]

Although we did not systematically review the comparators of interest for this appraisal, we searched for RCTs of natalizumab, beta interferons, and ocrelizumab in patients with progressive disease in an attempt to conduct indirect treatment comparisons of these agents compared to siponimod. As noted above, differences in study demographics, outcomes assessment, and treatment paradigm shifts precluded any kind of indirect treatment comparison. However, evidence from the identified RCTs of beta interferons, natalizumab, and ocrelizumab are summarized in the sections that follow for context and a few key studies are presented in Table 3.1 below. Details of all included studies are presented in Appendix Tables D1-D6.

Table 3.1. Key Studies

Study & MS Population	Patient Characteristics	Treatment	Comparator	Between Treatment Differences
Kappos 2018[19] **EXPAND** **SPMS**	Age, mean (SD): 48.0 (7.8) years EDSS, mean (SD): 5.4 (1.1) Time since MS Dx, mean (SD): 12.9 (7.9) years Time since conversion to SPMS, mean (SD): 3.9 (3.6) years Number of relapses in 2 years prior to screening, mean (SD): 0.7 (1.2)	**Siponimod** (n=1105)	**Placebo** (n=546)	
		CDP-3, n/N (%): 288/1096 (26%)	CDP-3, n/N (%): 173/545 (32%)	HR (95% CI): 0.79 (0.65, 0.95) p=0.013 NNT_3: 17***
		ARR, adj. mean (95% CI): 0.07 (0.06, 0.09)	ARR, adj. mean (95% CI): 0.16 (0.12, 0.21)	RR (95% CI): 0.45 (0.34, 0.59) p<0.0001
		D/C due to AEs, n (%): 84 (8)	D/C due to AEs, n (%): 28 (5)	NR
Kappos 1998[21,80] **E.U.** **SPMS**	Age, mean (SD): 41.1 (7.2) years EDSS, mean (SD): 5.1 (1.1) Disease duration, mean (SD): 12.8 (6.6) years Time since SPMS Dx, mean (SD): 2.2 (2.4) years Relapse-free in 2 years prior to study, n (%): 115 (31.9)	**Interferon beta-1b** (n=360)	**Placebo** (n=358)	
		CDP-3, n (%): 140 (38.9%)	CDP-3, n (%): 178 (49.7%)	HR (95% CI): 0.70 (0.55, 0.88) p=0.007 NNT_3: 10***
		ARR, mean (95% CI): 0.44 (NR)	ARR, mean (95% CI): 0.64 (NR)	p=0.0002
		D/C due to AEs, n (%): 45 (12.5)	D/C due to AEs, n (%): 15 (4.2)	NR
Panitch 2004[22] **N. American** **SPMS**	Age, mean ± SEM: 46.1 ± 0.45 years EDSS, mean ± SEM: 5.2 ± 0.06 Duration of MS ± SEM: 14.6 ± 0.44 years Duration of SPMS ± SEM: 4.0 ± 0.19 years Relapse-free in 2 years prior to study, n (%): 170 (54)	**Interferon beta-1b 250 µg**[α] (n=317)	**Placebo** (n=308)	
		CDP-6, n (%): 101 (32%)	CDP-6, n (%): 105 (34%)	RR (95% CI): 0.93 (0.75, 1.17)[¥] p=0.610* NNT_6: 50***
		ARR (95% CI): 0.16 (NR)	ARR (95% CI): 0.28 (NR)	p=0.009
		D/C due to AEs, n (%): 28 (9)	D/C due to AEs, n (%): 12 (4)	NR
Kapoor 2018[30] **ASCEND** **SPMS**	Age, mean (SD): 47.3 (7.4) years EDSS, median (IQR): 6.0 (5.0-6.5) Time since MS symptoms, mean (SD): 16.8 (7.6) years Time since SPMS Dx, mean (SD): 4.7 (3.0) years Years since most recent relapse, mean (SD): 4.7 (4.1)	**Natalizumab** (n=439)	**Placebo** (n=448)	
		CDP-6_{EDSS}, n (%): 69 (16%)¤	CDP-6_{EDSS}, n/N (%): 67 (15%)¤	OR (95% CI): 1.06 (0.74, 1.53) p=0.753 NNT_6: 100***
		Adjusted ARR (95% CI): 0.08 (0.06, 0.10)	Adjusted ARR (95% CI): 0.17 (0.14, 0.21)	RR (95% CI): 0.453 (0.32, 0.63) p<0.001
		D/C due to AEs, n (%): 21 (4.8%)	D/C due to AEs, n (%): 21 (4.7%)	NR

Study & MS Population	Patient Characteristics	Treatment	Comparator	Between Treatment Differences
Hauser 2017[32,34] **OPERA I and OPERA II** **Relapsing MS**	Age, mean (SD): 40.2 (9.3) years† EDSS, mean (SD): 4.59 (0.6)† Time Since MS**Dx, mean (SD): 6.32 (5.7) years† Relapses in 2 years prior to enrollment, mean (SD): 1.87 (0.94)†	**Ocrelizumab** (n=175)†	**Interferon beta-1a** (n=180)†	
		CDP-3: 19.1†	CDP-3: 31.2†	HR (95% CI): 0.60 (0.38, 0.93)† p=0.022† NNT_6: 9***
		ARR, OPERA I (95% CI): 0.16 (0.12, 0.20)‡ ARR, OPERA II (95% CI): 0.16‡ (0.12, 0.20)	ARR, OPERA I (95% CI): 0.29 (0.24, 0.36)‡ ARR, OPERA II (95% CI): 0.29 (0.23, 0.36)‡	RR, OPERA I (95% CI): 0.54 (0.40, 0.72) p<0.001 RR, OPERA II (95% CI): 0.53 (0.40, 0.71) p<0.001
		D/C due to AEs, OPERA I, n (%): 13 (3.2)‡ D/C due to AEs, OPERA II, n (%): 16 (3.8)‡	D/C due to AEs, OPERA I, n (%): 26 (6.4)‡ D/C due to AEs, OPERA II, n (%): 25 (6.0)‡	NR
Montalban 2017[33] **ORATORIO** **PPMS**	Age, mean (SD): 44.7 (7.9) years EDSS, mean (SD): 4.7 (1.2) Time since onset of MS symptoms, mean (SD): 6.7 (4.0) y Time since PPMS Dx, mean (SD): 2.9 (3.2) years	**Ocrelizumab** (n=488)	**Placebo** (n=244)	
		CDP-3, n/N (%): 160/487 (32.9) CDP-6, n/N (%): 144/487	CDP-3, n/N (%): 96/244 (39.3) CDP-6, n/N (%): 87/244 (35.7)	HR (95% CI): 0.76 (0.59, 0.98) p=0.03 NNT_3: 16***
		ARR: NR	ARR: NR	NR
		D/C due to AEs, n (%): 20 (4.1)	D/C due to AEs, n (%): 8 (3.3)	NR

Baseline Patient characteristics reported for intervention arm only.

adj.: adjusted, AEs: Adverse Events, ARR: annualized relapse rate, CDP-3: 3-month confirmed disease progression, CDP-6: 6-month confirmed disease progression, D/C: discontinued, Dx: diagnosis, EDSS score: Expanded Disability Status Score, ITT : Intention to treat population, MS: multiple sclerosis, n = number of participants, NNT3: number needed to treat using CDP at three months, NNT6: number needed to treat using CDP at six months, NR: not reported, OR: odds ratio, RR: rate ratio, SD: standard deviation, SPMS: secondary progressive multiple sclerosis.

†: Data taken from the PIRA conference poster, ‡: data taken from ITT population in OPERA I and II main publication, α: reporting label dose arm, *: estimated using the Mantel-Haenszel method and a random effects model. **: in population at higher risk of SPMS, ***: calculated using the formula NNT= 1/(RiskPlacebo – RiskIntervention), ɣ: RR for 160µg and 250µg combined, ¤: the primary endpoint was a multi-component CDP. Results are reported for the EDSS component only.

Quality of Individual Studies

Using criteria from the US Preventive Services Task Force (USPSTF [See Appendix D]), we judged the EXPAND trial of siponimod to be good quality. This study was well-designed, had balanced baseline characteristics between arms, and used validated instruments to measure outcomes.

Clinical Benefits of Siponimod

Summary: *Siponimod reduced the risk of EDSS progression and decreased inflammatory disease activity, as measured by MRI outcomes and relapses. Significant benefits were not observed for other mobility-related measures, including the timed 25-foot walk test and the 12-point Multiple Sclerosis Walking Scale. Siponimod may have a small benefit on cognitive processing speed; data on MS symptoms, quality of life, mortality, caregiver burden, and health care utilization have not been reported. Pre-planned subgroup suggested that the risk of EDSS progression was most reduced in groups defined by recent relapse activity, rapid disease progression, and the presence of gadolinium-enhancing lesions.*

Evidence on siponimod was derived from the EXPAND trial.[19] This study was a multinational, double-blind, Phase III trial that randomized 1651 patients with SPMS to 2 mg once daily of oral siponimod (n=1105) or placebo (n=546). Patients were eligible to participate in the trial if they were 18-60 years of age, had received a diagnosis of SPMS (according to investigator attestation), and had a prior history of RRMS. Patients had to have an EDSS score of 3.0-6.5 and documented EDSS progression in the two years prior to screening of ≥ 1.0 point (or ≥ 0.5 points for patients with EDSS 6.0). SPMS was defined by a progressive increase in disability (of at least 6 months' duration) in the absence of, or independent of, relapses.

At baseline, the mean time since onset of MS symptoms was 16.8 years (standard deviation [SD] 8.3) and the mean time since conversion to SPMS was 3.8 years (SD 3.5). Almost two-thirds (64%) of patients had not relapsed in the two years prior to study enrollment; 21% had gadolinium-enhancing lesions on T1-weighted images, which is an indicator of recent active inflammation (within the last 2-3 months).

The EXPAND trial's primary endpoint was time to 3-month confirmed disability progression (CDP-3), defined as a 1.0-point increase in EDSS score (or 0.5-point increase if the patient's baseline EDSS was ≥ 5.5) confirmed at least three months later; six-month-CDP (CDP-6) was evaluated as a secondary endpoint.[19] Patients with CDP-6 had the option to switch to open-label siponimod or another DMT while remaining in the study. The median exposure to study drug was 18 months (range 0-37 months). Of the 1327 (80%) patients who completed the study, 102 (9%) and 77 (14%) of patients in the siponimod and placebo groups, respectively, switched to open-label siponimod.

Disability Progression

As noted above, EXPAND evaluated 3-month CDP as its primary endpoint. In the time-to-event analysis, siponimod reduced the risk of 3-month CDP by 21% (hazard ratio [HR]: 0.79; 95% CI 0.65 to 0.95; p=0.0134); 288/1096 (26%) patients in the siponimod group and 173/546 (32%) patients in the placebo group had CDP-3 (Table 3.2).[19] Results were consistent for 6-month CDP (HR: 0.74; 95% CI 0.60 to 0.92; p=0.0058).[19] Subgroup analyses of CDP-3 and CDP-6 suggest that participants who are older, with more advanced disability (higher EDSS score), longer disease duration, and less disease activity may derive a smaller benefit from siponimod, although differences were not statistically significant.

Table 3.2. Disability-Related Outcomes in the EXPAND Trial[19]

	Siponimod (n=1099)	Placebo (n=546)	Between-Group Difference (95% CI)	p-value
3-Month CDP	288/1099 (26%)	173/546 (32%)	HR 0.79 (0.65, 0.95)	0.013
6-Month CDP	218/1099 (20%)	139/546 (26%)	HR 0.74 (0.60, 0.92)	0.0058
Worsening ≥ 20% From Baseline in T25FW	432/1087 (40%)	225/543 (41%)	HR 0.94 (0.80, 1.10)	0.44
Worsening ≥ 20% From Baseline in T25FW, EDSS ≤ 5.5	145/478 (30%)	91/250 (36%)	HR 0.85 (0.65, 1.12)*	0.25
Adjusted Mean Change in MSWS-12 Score from Baseline				
Month 12	1.53 (0.20, 2.86)	3.36 (1.58, 5.14)	-1.83 (-3.85, 0.19)	0.076
Month 24	4.16 (2.49, 5.82)	5.38 (3.09, 7.67)	-1.23 (-3.89, 1.44)	0.37
Mean Over All Visits (Including Month 30)	2.69 (1.46, 3.92)	4.46 (2.82, 6.10)	-1.77 (-3.59, 0.05)	0.057

n/N (%) or adjusted mean (95% Confidence Interval)

CDP: confirmed disability progression, MSWS-12: 12 item Multiple Sclerosis Walking Scale, T25FW: timed 25-foot walk

*95% CI digitized from study publication and should be interpreted with caution

The EXPAND trial evaluated other mobility-related endpoints, including the timed 25-foot walk test (T25FW) and the 12-item Multiple Sclerosis Walking Scale (MSWS-12).[19] The T25FW measures gait velocity by averaging the time it takes a patient to complete two 25-foot walks that are spaced less than 5 minutes apart. Patients may use assistive devices to complete the walk. A change of 20% or more has been identified as clinically significant.[53] Whereas the T25FW is administered by trained assessors, the MSWS-12 is a patient-reported outcome that measures 12 components of an individual's walking ability. MSWS-12 scores range from 0-100, with higher scores indicating greater levels of walking disability. Several minimally clinically important differences have been suggested for the MSWS-12, ranging from 4 to 22, which are sensitive to the population and statistical approach taken.[81-84] In the EXPAND trial, significant differences were not observed in either the time to ≥20% worsening of T25FW or change in MSWS-12 score (see Table 3.2). A post

hoc analysis of patients who did not require an assistive device (i.e., EDSS ≤ 5.5) also did not demonstrate a statistically significant difference in the T25FW.

Disease Activity and MRI-related Outcomes

Patients in the siponimod arm of the EXPAND trial experienced significantly less inflammatory disease activity than patients in the placebo arm (see Table 3.3).[19] Siponimod reduced the risk of relapse by 46% (HR: 0.54; 95% CI 0.41 to 0.70; p<0.0001) and lowered the annualized relapse rate (0.07 vs. 0.16 for siponimod and placebo, respectively; p<0.0001). MRI-related outcomes showed that siponimod-treated patients had significantly fewer gadolinium-enhancing lesions on T1-weighted scans, fewer new or enlarging lesions on T2-weighted images, and less reduction in brain volume (Table 3.3).

Table 3.3. Disease Activity in the EXPAND Trial[19]

	Siponimod (n=1099)	Placebo (n=546)	Between-Group Difference (95% CI)	p-value
Annualized Relapse Rate (95% CI)	0.07 (0.06, 0.09)	0.16 (0.12, 0.21)	RR 0.45 (0.34, 0.59)	<0.0001
Time to First Confirmed Relapse	113/1061 (11%)	100/528 (19%)	HR 0.54 (0.41, 0.70)	<0.0001
Percent Brain Volume Change from Baseline, Adjusted Mean Over Months 12 and 24 (95% CI)	-0.50% (-0.55, -0.44)	-0.65% (-0.72, -0.58)	0.15% (0.07, 0.23)	0.0002
Patients with No T1 Gadolinium-Enhancing Lesions on All Post-Baseline Scans	917/1026 (89%)	341/510 (67%)	NR	NR
Patients with No New or Enlarging Lesions on T2-Weighted Images Over All Visits	584/1026 (57%)	190/510 (37%)	NR	NR
T1 Gadolinium-Enhancing Lesions Per Scan from Post-Baseline to Month 24, Adjusted Mean (95% CI)	0.08 (0.07, 0.10)	0.60 (0.47, 0.76)	RR 0.14 (0.10, 0.19)	<0.0001
New or Enlarging Lesions on T2-Weighted Images Over All Visits, Adjusted Mean (95% CI)	0.70 (0.58, 0.84)	3.60 (3.03, 4.29)	RR 0.19 (0.16, 0.24)	<0.0001

HR: hazard ratio, NR: not reported, RR: rate ratio

Progression Independent of Relapses

The question of whether siponimod delays progression independent of its effect on inflammatory disease activity is of interest to many stakeholders. In SPMS, disability can occur both as a result of incomplete relapse recovery as well as independent of relapse; relapse incidence, therefore, is a potential confounder of CDP results.

In the EXPAND trial, subgroups defined by the presence or absence of gadolinium-enhancing lesions and by the presence or absence of relapses in the prior two years (both associated with disease activity) were not statistically significantly different from each other, although in both cases the point estimates of effect were greater in patients with more active disease (HRs 0.64 vs 0.82 and 0.67 vs. 0.87, respectively; see Table 3.4). To evaluate whether siponimod affects CDP independent of relapses, Cree and colleagues conducted post hoc analyses using 3 different methods to control for the confounding impact of *on-study* relapses. In these analyses, the estimated risk reduction ranged from 14-18% for CDP-3 and 23-29% for CDP-6 (Table 3.4) for non-relapsing patients.[37] The results, some of which reached statistical significance, suggested a smaller but relatively consistent risk reduction amongst non-relapsing groups for disability progression with siponimod.

The FDA further explored the question of whether siponimod delays disability progression independent of relapses by conducting additional post hoc analyses in subgroups with and without relapses prior to the study, with and without relapses during the study, with and without gadolinium-enhancing lesions at baseline, and with and without new or enlarging lesions during the study (Table 3.5); the analyses also included a subgroup of patients who did not relapse in the two years prior to *or during* the study, some of whom did not have a relapse in almost 5 years.[20] The FDA concluded that these "analyses support the hypothesis that the delay in 3-month CDP is more clearly related to the anti-inflammatory effect of siponimod (yielding a significant treatment effect on the relapsing or active aspect of the disease) than to an effect on the poorly understood 'degenerative' process felt to [dominate] the pathophysiology of SPMS."[20]

Table 3.4. Disability Progression in Relapsing and Non-Relapsing Patients in the EXPAND Trial[19,37]

	3-Month CDP HR (95% CI)	6-Month CDP HR (95% CI)
CDP (Overall)	0.79 (0.65, 0.95)	0.74 (0.60, 0.92)
Prespecified Subgroup Analyses		
≥1 T1 Gadolinium-Enhancing Lesions at Baseline	0.64 (0.42, 0.95)*	0.59 (0.38, 0.92)*
0 T1 Gadolinium-Enhancing Lesions at Baseline	0.82 (0.66, 1.01)*	0.78 (0.61, 1.00)*
Relapses Within 2 Years of Enrollment	0.67 (0.49, 0.91)	0.63 (0.44, 0.89)*
No Relapses Within 2 Years of Enrollment	0.87 (0.68, 1.11)	0.82 (0.62, 1.08)*
Post Hoc Analyses to Control for On-Study Relapses		
Principal Stratum Analysis of Non-Relapsing Patients at 24 Months	0.82 (0.48, 1.32)	0.71 (0.37, 1.21)
Censoring at Relapse (Models Effect of Siponimod if No Relapse Observed)	0.86 (0.70, 1.04)	0.77 (0.62, 0.96)
Empirical Distribution Simulation (Assumes Same Relapse Rate in Both Treatment Arms)	0.82 (0.69, 0.99)	0.77 (0.63, 0.96)

n/N (%); CDP: confirmed disability progression

* 95% CI digitized from forest plot and should be interpreted with caution

Table 3.5. FDA Analyses of 3-Month Confirmed Disability Progression in Subgroups with Non-Active SPMS[20]

	Siponimod n (%)	Placebo n (%)	p-value	Siponimod n (%)	Placebo n (%)	p-value
	With			Without		
Relapses within 2 Years of Randomization	98 (25.3)	72 (35.6)	0.01	190 (26.8)	101 (29.4)	0.23
Relapses during Study	51 (45.1)	51 (50.0)	0.22	238 (24.1)	122 (27.5)	0.16
Gadolinium-Enhancing Lesions at Baseline	62 (26.3)	40 (35.1)	0.04	219 (26.4)	128 (30.8)	0.08
New/Enlarging T2 Lesions during Study	127 (28.7)	116 (36.3)	0.02	154 (26.4)	52 (27.4)	0.53
Relapses in 2 Years before Study or during Study	NA	NA	NA	169 (25.5)	76 (26.0)	0.66

Cognitive Function

The EXPAND trial evaluated the impact of siponimod on cognition and memory using the Symbol Digit Modalities Test (SDMT), Paced Auditory Serial Addition Test (PASAT), and Brief Visuospatial Memory Test Revised (BVMT-R); these scores were assessed as exploratory endpoints and were administered at 6-month intervals up to month 36.[85]

The SDMT examines an individual's cognitive processing speed by presenting the subject with a series of geometric symbols and asking them to use a key to translate the symbols to corresponding single-digit numbers.[51] A change in score of 4 points or 10% is considered clinically meaningful on the SDMT.[52] At month 24, patients treated with siponimod had statistically significantly better SDMT scores (between-group difference in adjusted mean=2.478; p-value=0.0004), although mean score changes did not reach clinically-meaningful thresholds.[85] Siponimod reduced the risk of a clinically meaningful deterioration in cognitive processing speed (i.e., ≥ 4 point change in SDMT) by 21% (HR=0.79; 95% CI 0.65 to 0.96; p=0.0157).

The PASAT and BVMT-R examine cognitive processing speed and memory, respectively. Statistical differences were not observed on either of these tests, although the subgroup of patients with

relapsing SPMS had significantly better PASAT scores (between-group difference in mean score=2.42; p=0.0275).[85]

Other Outcomes of Interest

We did not identify any data related to quality of life, mortality, caregiver burden, or health care utilization from the EXPAND trial. The effect of siponimod on symptoms of SPMS, including fatigue, depression, pain, bladder and bowel control, were not evaluated in the EXPAND trial.

Harms

Four deaths occurred in each treatment group of the EXPAND trial. In the siponimod group, these deaths were due to metastatic gastrointestinal melanoma, septic shock, urosepsis, and suicide; an additional patient with metastatic lung cancer died after withdrawing study consent, although the cause of death was unspecified.[19] Discontinuation of the study drug due to AEs was relatively low in the EXPAND trial and occurred in 8% of the siponimod group and 5% of the placebo group (Table 3.6).

Rates of non-fatal serious adverse events (AEs) were similar between groups (18% and 15% for the siponimod and placebo groups, respectively).[19] No individual serious AE occurred in > 1% of either patient group. The most frequently reported AEs were headache, nasopharyngitis, urinary tract infection, falls, and hypertension.

Bradycardia at treatment initiation, hypertension, lymphopenia, respiratory effects, infections, liver injury, and macular edema have been associated with S1P-receptor modulation.[40] These events were relatively uncommon in the EXPAND trial but occurred in proportionally more patients in the siponimod group (see Table 3.6). Infection rates were similar in both study groups. The FDA label for siponimod includes warnings about the risk of these events.[17]

Table 3.6. Adverse Events in the EXPAND Trial[19]

	Siponimod (n=1099), n (%)	Placebo (n=546), n (%)
Death	4 (<1)	4 (1)
Serious AEs	197 (18)	83 (15)
AEs Leading to Discontinuation	84 (8)	28 (5)
Headache	159 (15)	71 (13)
Nasopharyngitis	149 (14)	79 (15)
Urinary Tract Infection	133 (12)	80 (15)
Falls	128 (12)	59 (11)
Hypertension	115 (10)	41 (8)
Bradycardia at Treatment Initiation	48 (4)	14 (3)
Lymphopenia	9 (1)	0
Macular Edema	18 (2)	1 (<1)
Infections and Infestations	539 (49)	268 (49)
Herpes Viral Infections	53 (5)	15 (3)

AEs: adverse events

Siponimod in RRMS

While relapsing-remitting multiple sclerosis (RRMS) was not the focus of this report, the FDA recently approved siponimod for the treatment of relapsing forms of MS, which includes RRMS, active secondary progressive MS and clinically isolated syndrome.[17] In order to provide additional evidence relevant to siponimod's labeled indication, we summarize the Phase II BOLD trial of siponimod in patients with RRMS.[86]

The BOLD study was a multicenter, randomized trial that evaluated the dose-response relation of siponimod in RRMS patients. Although several doses of siponimod were evaluated in the study, we summarize only the findings relevant to the FDA-approved dose (2 mg). Patients who enrolled in the study were between 18-55 years of age, had an EDSS score ≤5.0, had at least one documented relapse in the year prior to enrollment and at least two documented relapses in the two years prior to the study, or ≥1 gadolinium enhancing lesion(s) at screening.

One-hundred-eleven participants were randomized to once daily 2mg siponimod (n=49) or matching placebo (n=62) and followed for six months.[86] At baseline, the mean age for the siponimod arm was 37.4 (SD 8.9) years, the mean time since onset of MS symptoms was 7.2 (6.8) years, and the mean EDSS score was 2.4 (1.2). On average, patients experienced 1.3 (0.6) relapses in the previous year and 2.1 (1.0) in the two years prior to the study. Sixty-nine percent of participants randomized to the siponimod arm were female and 54% had gadolinium-enhancing lesions.

Siponimod significantly reduced the number of monthly new gadolinium-enhancing lesions and new or newly enlarged T2 lesions at both three and six months (Table 3.7).[86] In addition, siponimod

significantly reduced the annualized relapse rate (ARR) compared to placebo at six months (Table 3.7). The proportion of patients who stayed relapse-free after 6 months of treatment was numerically higher in the siponimod group (90%) versus the placebo group (79%), although statistical differences were not tested. The observed treatment effects were sustained at similar levels throughout the dose-blinded, randomized extension phase.[87]

Table 3.7. Efficacy Outcomes in the BOLD trial[86]

	3 Months, Estimated Number (95% CI)			6 Months, Estimated Number (95% CI)		
	Siponimod† (n=45)	Placebo (n=61)	p-value	Siponimod† (n=45)	Placebo (n=45)	p-value
Monthly New Gadolinium-Enhancing Lesions	0.40 (0.19, 0.81)*	1.29 (0.72, 2.32)*	p=0.0119	0.38 (0.15, 0.92)*	1.65 (0.99, 2.69)*	p=0.0051
Monthly New or Newly Enlarged T2 Lesions	0.40 (0.20, 0.81)*	1.47 (0.86, 2.53)*	p=0.0049	0.41 (0.19, 0.95)*	2.09 (1.26, 3.49)*	p=0.0012
Annualized Relapse Rate	NR			0.20 (0.08, 0.48)*	0.58 (0.34, 1.00)*	p=0.0408

*Digitized from study publication and should be interpreted with caution. †only reporting on results from the FDA approved dose (2 mg). Outcomes were analyzed using a negative binominal generalized regression model.

At 6 months, six patients (12%) in the siponimod arm and two patients (4%) in the placebo group discontinued treatment due to adverse events. Serious adverse events were reported by 8% in the siponimod arm, while none were reported in the placebo arm. AEs that were more commonly reported by siponimod-treated patients included headaches (31% vs. 9% in the placebo arm), bradycardia (6% vs 2% in the placebo arm), and second-degree atrioventricular block (6% vs. 4% in the placebo arm). Alanine aminotransferase levels increased in four patients (8%) treated with siponimod, whereas no increases were reported in patients in the placebo group.

Clinical Benefits of Comparator Therapies

Beta Interferons

Our literature review identified two trials of interferon beta-1b in patients with SPMS. The European trial was a three-year study that randomized 718 SPMS patients to receive interferon beta-1b or placebo.[21] In this study, interferon beta-1b demonstrated a statistical benefit on CDP, as well as mean annual relapse rate, T2 lesion volume, and reduction of newly active lesions. A similarly designed study, the North America SPMS trial (n=939), also resulted in improvements on

measures of clinical relapse and newly active MRI lesions, but showed no progression benefit with interferon beta-1b.[22] The EU trial population was younger, with a shorter disease duration and more active disease, suggesting that patients with ongoing relapse activity may be more likely to benefit from interferon beta-1b.[23]

We also identified three trials of interferon beta-1a in SPMS populations, namely, SPECTRIMS, Nordic SPMS, and IMPACT. Neither SPECTRIMS nor the Nordic SPMS trials demonstrated a progression benefit with treatment, although the Nordic study examined low-dose (22 µg once weekly) interferon beta-1a in patients with less active SPMS.[24,25] The IMPACT trial reported a 40.4% reduction in median MS Functional Composite z-score, which was comprised of the T25FW, Nine-Hole Peg Test ([9HPT] arm function), and PASAT (cognition), in patients randomized to interferon beta-1a (-0.096 vs. -0.161; p=0.033). This effect was driven primarily by the Nine-Hole Peg Test and the PASAT results.[26] Patients in the interferon beta-1a group had less relapse and MRI activity but no differences were observed between groups in EDSS progression (defined as a 1.0-point increase for baseline EDSS ≤ 5.5 and a 0.5-point increase for baseline EDSS 6.0 to 6.5) or mean change in EDSS score.

Common adverse events associated with beta interferons include injection site reaction, lymphopenia, flu-like symptoms, myalgia, leukopenia, neutropenia, elevated liver enzymes, headache, hypertonia, pain, rash, insomnia, abdominal pain, and asthenia.[27-29]

Natalizumab

We identified a single Phase III RCT (ASCEND) of natalizumab in patients with SPMS (n=889).[30] At baseline, the mean time since first MS symptoms was 16.5 years (SD 7.7) and the mean time since conversion to SPMS was 4.8 years (SD NR); 71% of patients were relapse-free in the two years prior to baseline, and a mean of 4.8 years had passed since the most recent relapse.

The ASCEND trial's primary outcome was defined as the proportion of patients with sustained disability progression on one or more measures: the EDSS, T25FW, and Nine-Hole Peg Test. No treatment effect was observed on the composite endpoint, nor on the EDSS or T25FW components. However, 9HPT-defined progression was nominally significant, with 15% and 23% in the natalizumab and placebo groups, respectively, experiencing a deterioration in upper-limb function (odds ratio [OR]: 0.56; 95% CI 0.40 to 0.80; p=0.001).[30] Treatment benefits were not observed on other secondary endpoints, including the MSWS-12, measures of upper limb manual ability (ABILHAND), impact of MS on daily living (MSIS-29), and percentage change in whole brain volume, although relapse rates and other MRI outcomes improved with natalizumab.

The prescribing information for natalizumab includes a black box warning for progressive multifocal leukoencephalopathy (PML), a viral brain infection that can lead to severe disability or death.[31] Natalizumab's prescribing information also warns of herpes infections, liver toxicity,

hypersensitivity reactions (including anaphylaxis), and immunosuppression and infections. The most common AEs (≥ 10%) associated with natalizumab are headache, fatigue, arthralgia, urinary tract infection, lower respiratory infection, gastroenteritis, vaginitis, depression, extremity pain, abdominal discomfort, diarrhea, and rash.

Ocrelizumab

We did not identify any studies of ocrelizumab in patients with a documented diagnosis of SPMS. Results from the MS Coalition survey (described in Section 1.4) suggest that ocrelizumab is currently one of the most-used therapies in SPMS. Twenty-two percent of survey respondents reported that they currently take ocrelizumab for their SPMS, whereas none of the other DMTs were selected by more than 6% of respondents as being their current therapy. As such, the comparative clinical effectiveness of ocrelizumab in SPMS is of interest to stakeholders. There have been randomized trials of ocrelizumab in relapsing forms of MS (OPERA-I and OPERA-II) and in PPMS (ORATORIO).[32,33] We heard from clinical experts that an agent that works in both these groups is likely to work in SPMS, given that patients with SPMS may still be relapsing (RMS) or be in a purely progressive stage of the disease (similar to PPMS).

The OPERA I and OPERA II trials were two identical Phase III trials that randomized 1656 patients with relapsing MS to receive 600 mg of intravenous ocrelizumab every 24 weeks or 44 µg of subcutaneous interferon beta-1a three times a week over 96 weeks.[32] Patients were required to have an EDSS score ≤ 5.5, at least two relapses within the previous two years (or one within the past year), and evidence of MS on imaging in order to be eligible for the study. Although SPMS patients were not excluded from the study, physician assessment of whether a patient was in the RRMS or SPMS course of MS was not collected at baseline. In the overall population of both trials, ocrelizumab demonstrated a treatment benefit relative to interferon beta-1a with respect to relapse rates, CDP-3 and CDP-6, and MRI-related measures.

A post hoc subgroup analysis that pooled data from both OPERA-I and OPERA-II attempted to assess patients who were at higher risk of SPMS based on an EDSS score ≥4 and pyramidal function system Score ≥2.[34] Importantly, investigators relied on a surrogate definition of SPMS, which did not account for whether patients had sustained disability progression in the absence of relapse. It is possible, therefore, that some of the patients included in the analysis were misclassified.

Patients characterized as being at higher risk of SPMS had a mean age of 41, mean baseline EDSS score of 4.6, and had received their MS diagnosis approximately 6.4 years prior to the study. The subgroup experienced an average of 1.4 relapses in the prior year and 36% had T1 gadolinium-enhancing lesions.

Study investigators evaluated a composite CDP, defined as disability progression measured by EDSS (increase ≥ 1.0 if baseline EDSS ≤ 5.5 or 0.5 if baseline EDSS > 5.5), ≥ 20% increase in the T25FW, or

≥ 20% increase in the 9HPT.[34] In order to evaluate disability progression independent of relapse activity (PIRA), investigators re-baselined EDSS, T25FW, and 9HPT reference assessments at least 30 days after each relapse so that no relapses occurred between the reference assessment and the initial disability progression event. The results of this analysis suggested that ocrelizumab reduced the risk of 12- and 24-week confirmed composite PIRA by 40% and 36%, respectively (Table 3.8). However, as described above, these patients had highly active relapsing disease and were retrospectively labeled as "likely SPMS" without confirmation from a clinician. Consequently, it is uncertain how representative these results are of what would happen in a prospectively defined population with SPMS.

Table 3.8. Progression Independent of Relapse Activity in Patients at Higher Risk of SPMS in the OPERA I and OPERA II Trials of Ocrelizumab*[34]

	Ocrelizumab (n=175), %	Interferon Beta-1a (n=180), %	Hazard Ratio (95% CI)	p-value
12-Week Confirmed				
Composite PIRA	19.1	31.2	0.60 (0.38, 0.93)	0.022
EDSS-PIRA	3.7	8.9	0.45 (0.18, 1.09)	0.071
T25FW-PIRA	15.5	22.6	0.65 (0.38, 1.11)	0.1
9HPT-PIRA	3.8	8.5	0.46 (0.17, 1.23)	0.1
24-Week Confirmed				
Composite PIRA	16.6	26.9	0.64 (0.39, 1.03)	0.063
EDSS-PIRA	3.7	7.5	0.54 (0.21, 1.35)	0.2
T25FW-PIRA	13.4	19.2	0.70 (0.39, 1.24)	0.2
9HPT-PIRA	3.2	7.1	0.47 (0.16, 1.37)	0.2

9HPT: 9-hole peg test, EDSS: Expanded Disability Status Scale, PIRA: progression independent of relapse activity, T25FW: timed 25-foot walk

*data presented at ECTRIMS meeting in 2017

Cognition in patients deemed to be at increased risk of progressive disease was evaluated in another pooled analysis of the OPERA trials using the Symbol Digit Modalities Test (SDMT). A significantly greater mean (SE) improvement was reported with ocrelizumab (6.2 [1.2]) vs. interferon beta-1a (2.6 [1.2]; p=0.023) over 96 weeks.[88] The proportions of patients who achieved clinically meaningful improvements (≥ 4 points or ≥ 10%) on the SDMT were greater in the ocrelizumab group than in the interferon beta-1a group (Table 3.9).

Table 3.9. Clinically Meaningful Improvement on Symbol Digital Modalities Test in OPERA I and II Trials of Ocrelizumab[88]

Threshold	Ocrelizumab (n=186), %	Interferon Beta-1a (n=180), %	p-value
≥ 4 points	62.2	46.5	0.009
≥ 10%	60.1	43.4	0.006

The phase III ORATORIO trial randomized 732 patients with PPMS to ocrelizumab or placebo for a minimum of 120 weeks.[33] Participants had a mean age of 44 years, the mean time since they received their PPMS diagnosis was 2.9 years, 88% had not used any previous DMTs, 27% had T1 gadolinium-enhancing lesions, and the mean EDSS score was 4.7.

The primary endpoint was the percentage of patients with CDP-3, defined as an increase ≥1.0 if baseline EDSS ≤ 5.5 or 0.5 if baseline EDSS > 5.5).[33] 32.9% of patients in the ocrelizumab group versus 39.3% of patients in the placebo group had confirmed disability progression (HR: 0.76; 95% CI 0.59 to 0.98; p=0.03); results of CDP-6, which was evaluated as a secondary endpoint, were consistent (HR: 0.75; 95% CI 0.58 to 0.98; p=0.04). Patients treated with ocrelizumab had less deterioration in their performance on the T25FW than patients in the placebo arm (mean change from baseline: 38.9% with ocrelizumab vs. 55.1% with placebo; p=0.04) and had a lower risk of 24-week confirmed progression ≥ 20% on the T25FW (HR: 0.73; 95% CI 0.59 to 0.91; p=0.006). Similarly, 24-week confirmed progression on the 9-hole peg test by ≥ 20% occurred in fewer patients treated with ocrelizumab versus placebo (14.1% vs. 23.4%, respectively; HR: 0.55; 95% CI 0.38 to 0.77; p<0.001). MRI endpoints showed significantly less brain volume loss and lesion burden with ocrelizumab.

Common side effects associated with ocrelizumab include infusion reactions, upper and lower respiratory tract infections, and skin infections.[35] Ocrelizumab's prescribing information also includes a warning about an increased risk of malignancy.

Collectively, the evidence for ocrelizumab in relapsing and primary progressive MS suggest that ocrelizumab is a well-tolerated therapy that delays progression and decreases disease activity in both populations. Given its effectiveness in relapsing and progressive patients, it seems plausible that ocrelizumab would also benefit an SPMS population. However, differences in trial populations and study designs prevent us from being able to quantify the net health benefit of ocrelizumab in SPMS.

Despite similarities in the natural history of primary and secondary progressive MS, these disease courses have some pathophysiologic differences. Additionally, patients in the ORATORIO trial had a shorter disease duration compared to patients who participated in trials of the other therapies we reviewed (approximately 7 years vs. 13-17 in the SPMS trials of siponimod, natalizumab and beta interferons), lower baseline EDSS (4.7 vs. 5.1-6.0), younger age, and no relapse history. Similarly, the patients deemed at higher risk of SPMS in the OPERA I and OPERA II trials of relapsing MS had a

shorter disease duration but more active MS course than those who participated in the other trials included in this review. The "likely SPMS" subgroup was classified retrospectively in a post hoc analysis of progression and made up a small subset of the overall trial population. Whereas other trials included in our review compared an active agent to placebo, the OPERA trials compared ocrelizumab to interferon beta-1a.

In sum, it is uncertain whether patients with SPMS would derive a better, worse, or similar benefit from ocrelizumab as the patients with PPMS who participated in ORATORIO and the patients with RMS who participated in OPERA I and II.

Controversies and Uncertainties

As discussed in Section 1.1, distinguishing between relapsing-remitting and secondary progressive MS is challenging, as the phenotypes often overlap and the transition from RRMS to SPMS is only evident retrospectively. In clinical practice, uncertainty surrounding the transition from RRMS can result in a delay in SPMS diagnosis of approximately three years.[36] Enrollment in the EXPAND trial was predicated on investigator attestation that a patient had at least 6 months of progressive increase in disability in the absence of, or independent of, relapses; these attestations were not collected at several study sites. In addition, almost 80% of enrolled patients were on a previous MS medication, which can mask inflammatory disease without a sufficient washout period.[20] Clinical experts and the FDA noted that this left open the possibility for misclassification of some patients.

Several DMTs have been studied in primary and secondary progressive MS but, with the exception of ocrelizumab, have largely failed to demonstrate an effect on disability progression.[16,22,24-26,30,33] The statistically significant CDP results that were observed in the EU trial of interferon beta-1b were attributed to the enrollment of a younger patient population that had a shorter disease duration and more active MS; subsequent trials of beta interferons in patients with more advanced disease reported negative results.[21-23,25,26]

Subgroup analyses in the EXPAND trial of siponimod demonstrated several findings that need further substantiation. A larger effect size in CDP-3 was observed in patients with active disease (i.e., those with recent relapses or gadolinium-enhancing lesions) relative to those with non-active MS.[19] In subgroups defined by older age, longer disease duration, the absence of gadolinium-enhancing lesions, and the absence of relapse in the two years prior to enrollment, CDP results were not statistically significant. However, the confidence intervals associated with these subgroups were wide and the point estimates suggested a relatively consistent, albeit diminished, reduction in the risk of disability progression. Additional post hoc analyses applied three different statistical methods to evaluate the effect of siponimod independent of relapse activity.[37] These analyses suggested that siponimod may have a small effect on neurodegenerative processes. However, when the FDA reviewed these post hoc analyses and conducted a few additional analyses of their own (e.g., in the subgroup of patients who did not relapse in the two years prior to

enrollment *or* during the study and in the subgroup with no new or enlarging T2 lesions during the study), they concluded that there was insufficient evidence to support the approval of siponimod for the full SPMS population.[20] Further study is required to confirm that siponimod is an effective therapy for patients who no longer have inflammatory disease activity or relapses.

As noted, the US FDA chose not to approve siponimod for non-active SPMS. The FDA was concerned that EXPAND failed to meet its "key" secondary endpoint, time to 3-month confirmed 20% worsening on the Timed 25 Foot Walk.[20] The EDSS is heavily weighted toward ambulatory dysfunction, particularly in the EDSS scores recruited for the trial (median EDSS=6), making it surprising that the trial would meet its EDSS progression endpoint but not the T25FW. The results of the T25FW have been directionally consistent with the results of EDSS progression in other studies in progressive MS.[16,30,38]

FDA reviewers were also concerned about the conduct of the EXPAND trial.[20] As noted above, investigator attestations that patients had SPMS were not collected. In addition, a "dual database access issue" occurred, which may have led to the unblinding of 101 subjects. When the disability scores for these individuals were excluded from the analysis of CDP-3, the treatment effect was smaller (relative risk reduction of 17%, p=0.062).

The FDA considered the 6% absolute risk reduction conferred by siponimod in CDP-3 in the primary endpoint analysis to be a modest treatment benefit.[20] It is uncertain if this small change in disability progression will translate into changes in clinical outcomes that are meaningful to patients. The EXPAND trial did not evaluate many patient-reported outcomes, and quality of life measurements were conspicuously absent from the results. Patient advocacy groups expressed a strong interest in the systematic measurement of patient-reported outcomes in SPMS and the incorporation of such metrics into clinical trials and economic models. Measurements are desired in the domains of caregiver burden, costs (personal, familial, societal) of disability, mental health, cognition, vision, upper limb function, pain, fatigue, bowel/bladder issues, family relationships, and quality of life. Of note, the Accelerated Cure Project is working to develop, validate, and standardize a core set of patient-reported outcomes in MS across countries and cultures.

Long-term safety data for siponimod are not yet available. New therapies frequently have important side effects discovered after FDA approval.[39] The FDA prescribing information for fingolimod, another sphingosine-1-phosphate receptor modulator that was approved for relapsing MS, includes several warnings for serious adverse effects, which include progressive multifocal leukoencephalopathy (PML), posterior reversible encephalopathy syndrome, liver Injury, malignancies, and a severe increase in disability after discontinuation of fingolimod.[40] These adverse events were not reported or did not occur disproportionately in siponimod-treated patients in the EXPAND trial, but the median exposure to siponimod was only 18 months. Conversely, the median observation period in the core double blind trial period (21 months) may have been too short to see the full outcome benefit of treatment compared to placebo. Longer term data from an

ongoing seven-year open-label extension of EXPAND may provide further evidence on the efficacy and safety of siponimod.

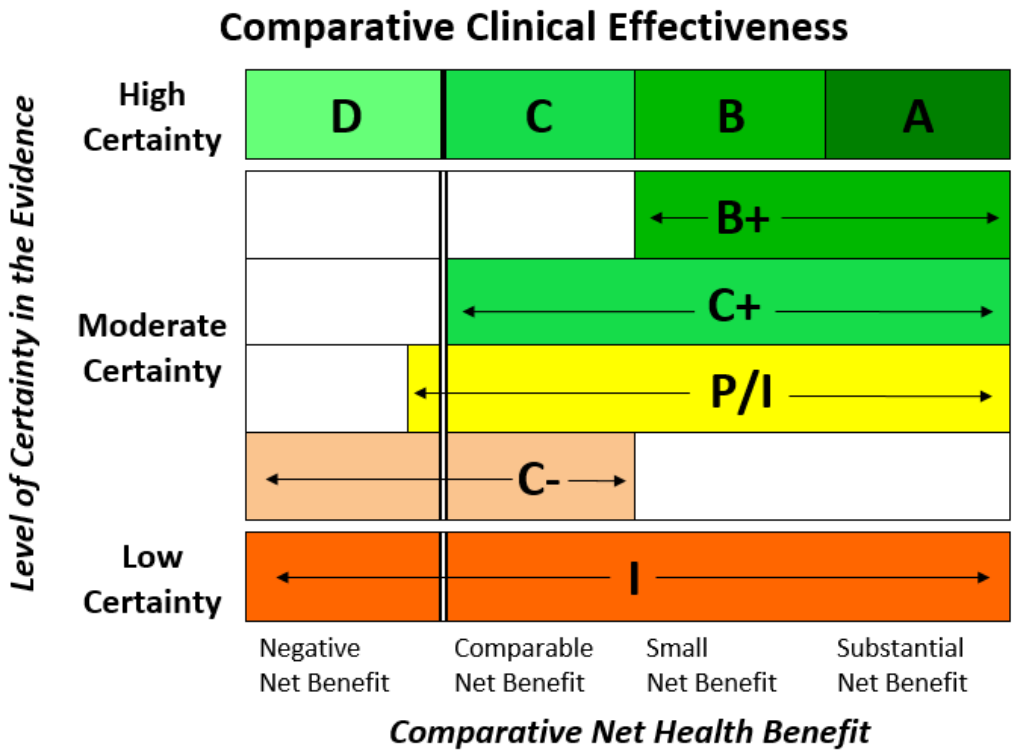
Finally, there are a lack of comparative effectiveness data in the form of head-to-head trials between DMTs in SPMS. In the absence of randomized trials where treatment and adverse events can be directly compared between medications, indirect comparisons using network-meta analysis (NMA) can sometimes be performed to estimate comparative benefit. However, for reasons explained in Section 3.3, performing an NMA was not possible. The comparison of siponimod to ocrelizumab was of particular interest for this review because of the high utilization of ocrelizumab in SPMS and perceived effectiveness of this agent across different MS phenotypes. As noted in Section 3.3, results from trials in relapsing MS patients (OPERA I and OPERA II) and primary progressive MS patients (ORATORIO), which showed that ocrelizumab is effective in patients with inflammatory disease activity and in patients with a purely progressive phenotype, lend plausibility that ocrelizumab would also provide a benefit to patients with SPMS. However, differences in trial populations and pathophysiologic differences between relapsing MS, PPMS, and SPMS, challenge our ability to extrapolate from the existing trials of ocrelizumab. Therefore, while we believe it is likely to be an effective therapy for SPMS, we remain uncertain about the magnitude of benefit it would provide and whether it would be superior, inferior, or comparable to siponimod.

3.4 Summary and Comment

Using the ICER Evidence Matrix (Figure 3.1), we assigned evidence ratings to siponimod relative to best supportive care in patients with active disease (i.e., ongoing relapse activity, the presence of new or enlarging lesions on MRI, or gadolinium-enhancing lesions on MRI) and non-active secondary progressive multiple sclerosis (Table 3.10). It should be noted that the primary outcome in the EXPAND trial was CDP-3 for *all* SPMS patients regardless of disease activity, although the investigators did pre-specify subgroup analyses for patients with and without relapses in the 2 years prior to trial enrollment and with and without gadolinium-enhancing lesions at baseline. Expert opinion as well as studies of fingolimod led us to conclude that the prior probability of efficacy in active SPMS (a relapsing form of MS) was higher than in non-active SPMS. As such, uncertainties surrounding the net health benefit of siponimod in patients with non-active disease led us to assign discrete evidence ratings to each of these subgroups. The FDA seems to have similarly found differences in the evidence base for the use of siponimod in active and non-active SPMS.

The lack of head-to-head data as well as our inability to indirectly compare siponimod to other DMTs through network meta-analysis precluded assessment of the comparative net health benefit of siponimod relative to beta interferons, natalizumab, or ocrelizumab.

Figure 3.1. ICER Evidence Rating Matrix



A = "Superior" *- High certainty of a substantial (moderate-large) net health benefit*
B = "Incremental" *- High certainty of a small net health benefit*
C = "Comparable" *- High certainty of a comparable net health benefit*
D = "Negative" *- High certainty of an inferior net health benefit*
B+ = "Incremental or Better" *- Moderate certainty of a small or substantial net health benefit, with high certainty of at least a small net health benefit*
C+ = "Comparable or Better" *- Moderate certainty of a comparable, small, or substantial net health benefit, with high certainty of at least a comparable net health benefit*
P/I = "Promising but Inconclusive" *- Moderate certainty of a comparable, small, or substantial net health benefit, and a small (but nonzero) likelihood of a negative net health benefit*
C- = "Comparable or Inferior" *- Moderate certainty that the point estimate for comparative net health benefit is either comparable or inferior*
I = "Insufficient" *- Any situation in which the level of certainty in the evidence is low*

Table 3.10. ICER Evidence Ratings

Intervention	Comparator	Population	ICER Evidence Rating
Siponimod	Best supportive care	Active SPMS	B+
Siponimod	Best supportive care	Non-active SPMS	I

Siponimod Versus Best Supportive Care in Patients with Active SPMS

Compared to best supportive care (i.e., placebo), siponimod significantly reduced the risk of EDSS-defined disability progression and decreased inflammatory disease activity, as measured by MRI outcomes and relapses in the overall trial population. In subgroup analyses of patients who experienced recent relapses and patients with at least one T1 gadolinium-enhancing lesion at baseline, the reduction in the risk of 3-month confirmed disability progression was at least as good as in the overall population and perhaps better.

Siponimod did not show a significant effect on other outcomes related to progression and ambulation, such as the T25FW and 12-point MS Walking Scale. Exploratory analyses failed to show a clinically meaningful benefit for siponimod on cognition and memory, and the effect of siponimod on quality of life or other MS symptoms were not reported in the EXPAND trial. Nevertheless, the therapy was well-tolerated and unlikely to adversely affect quality of life.

Although the degree to which siponimod delays progression independent of its effect on relapse activity remains uncertain, it is known that poor recovery from relapses can contribute to disability progression in MS. We have high certainty, therefore, that siponimod provides at least a small net health benefit in patients with active SPMS compared to best supportive care ("B+").

Siponimod Versus Best Supportive Care in Patients with Non-Active SPMS

In the subgroup of patients without relapses in the two years prior to the EXPAND study, the point estimate of benefit with siponimod was lower than in the group as a whole, although the differences were not statistically significant. Relapse incidence is a potential confounder of CDP results. To evaluate whether siponimod affects CDP independent of relapses, EXPAND trial investigators conducted post hoc exploratory analyses to control for the confounding impact of *on-study* relapses. The results, some of which reached statistical significance, suggested a relatively consistent risk reduction for disability progression with siponimod.[37] However, the FDA's review of siponimod revealed that elements of the EXPAND trial's conduct (e.g. failure to collect investigator attestations of SPMS), as well as findings from additional post-hoc analyses of progression, lend additional uncertainty about whether siponimod confers a benefit in non-active SPMS As such, we find the evidence insufficient to determine siponimod's net benefit compared with best supportive care in patients with non-active SPMS ("I").

Siponimod Versus Comparators

In the absence of head-to-head or indirect treatment comparisons of siponimod versus beta interferons, natalizumab, or ocrelizumab, we have insufficient data ("I") to conclude that the net health benefit of siponimod is superior/inferior to any of these other DMTs in patients with SPMS.

4. Long-Term Cost Effectiveness

4.1 Overview

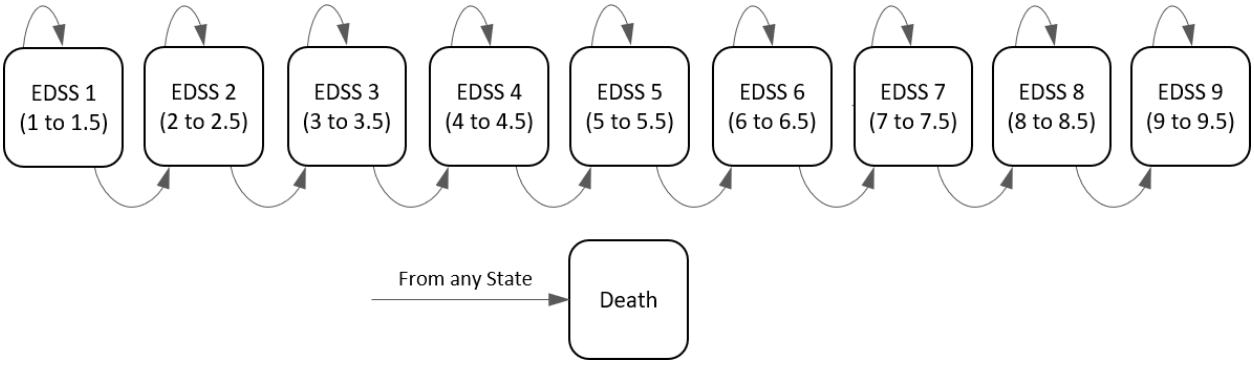
The primary aim of this analysis is to estimate the cost effectiveness of siponimod for the treatment of SPMS in the overall SPMS population and the subpopulation with active SPMS, i.e., patients with evidence of relapses within two years of enrollment. The model compares siponimod to best supportive care (BSC), informed by the placebo arm of the siponimod clinical trial.[19] As a separate scenario analysis, siponimod was compared to a DMT which has been studied in SPMS patients based on the results of a matching-adjusted indirect comparison (MAIC) submitted by the manufacturer as academic in confidence data.[89] A scenario was also conducted for the subgroup of patients with non-active disease. The model was developed leveraging previously published work evaluating the cost effectiveness of MS treatments, using a Markov model with health states based on Expanded Disability Status Scale (EDSS) score.[41,42,45,90,91] The base-case analysis takes a health care sector perspective with focus on direct medical care costs only. The model used a lifetime horizon, with a discount rate of 3%. The indirect cost of MS, including productivity losses and caregiver burden, were considered in a societal perspective scenario analysis. The model was developed in Microsoft Excel Office 365 (version 1903).

4.2 Methods

Model Structure

The model is structured as a Markov model consisting of nine health states based on the EDSS, and death, with a cycle length of one year (Figure 4.1). Although few economic models have been developed specifically for SPMS,[90-94] several relapsing-remitting MS (RRMS) models have included the transition from RRMS to SPMS and the clinical course thereafter.[41,42,45,95-106] These models have predominantly chosen to model SPMS using a similar Markov cohort model structure and cycle length.

Figure 4.1. Model Framework



At baseline, patients are distributed across the nine EDSS-based health states according to the baseline distribution in the siponimod clinical trial.[19] Patients then transition between health states during each one-year cycle over a lifetime time horizon. Over time, a patient's EDSS score may increase or remain the same but will not decrease. A patient can progress to death or have a relapse from any state. After treatment discontinuation, the patient receives best supportive care and transitions according to the natural history of SPMS.

Each EDSS health state was associated with a risk of relapse, utility, risk of mortality, and direct costs. The discontinuation rate for siponimod was based on the observed discontinuation rates from the clinical trial (years 1 and 2) and an assumed rate of 3% per year thereafter, which was used in previous analyses.[19,107] A stopping rule was included in the active disease subgroup analysis based on the assumption that patients would use siponimod for the approved use in active disease and discontinue when the disease transitions to non-active SPMS. The stopping rule was set at EDSS 7 based prior models of DMTs in MS and in alignment with a reduction in relapse activity at EDSS 7.[41,42,44,107] Alternative stopping rules were explored in sensitivity analysis.

For each therapy, total drug cost was calculated including acquisition, administration, and monitoring costs. Each health state has additional direct costs, including inpatient care, ambulatory care, tests, prescription drugs other than DMTs, and investments in additional resources for care (e.g., a wheelchair and mobility services). Finally, a cost was included for the occurrence of relapses.

Target Population

The base case population considered in this review was adults aged ≥ 18 years with SPMS. We considered both the overall SPMS population in which siponimod was investigated as part of the EXPAND trial and the subgroup of SPMS patients with evidence of relapses within two years of enrollment (used as a proxy for active SPMS). This subpopulation was evaluated due to the suggestion in the trial data of differential treatment effects, as well as the FDA's recent approval of siponimod for patients with active SPMS. An analysis of the subgroup of patients with non-active SPMS was included as a scenario analysis.

The baseline population characteristics mirror those of the EXPAND trial. At baseline, 0.5% of patients had EDSS score < 3, 27.9% had EDSS 3.0-4.5, 16.1% had EDSS 5.0-5.5, 55.4% had 6.0-6.5, and 0.2% had EDSS > 6.5. As the available baseline distribution is not broken down by individual EDSS health states, several assumptions were made, as outlined in Table 4.1.

Table 4.1. Base-Case Model Cohort Characteristics

	Value	Primary Source
Mean (SD) Age	48 (4.8) years	[19]
Female	61%	[19]
EDSS Distribution		
1	0.0%	Estimated based on categorical percentages[19]
2*	0.5%	
3**	14.0%	
4**	14.0%	
5	16.1%	
6	55.3%	
7†	0.2%	
8	0.0%	
9	0.0%	

*All patients with EDSS < 3 will be assumed to be in health state EDSS = 2 (2.0-2.5).
** The EDSS score 3.0-4.5 contains both EDSS 3 (3.0-3.5) and EDSS 4 (4.0-4.5). The 27.9% in 3.0-4.5 at baseline were assumed to be divided equally into EDSS 3 and 4.
† All patients with EDSS > 6.5 will be assumed to be in health state EDSS = 7 (7.0-7.5).
EDSS: Expanded Disability Status Scale, SD: standard deviation

Treatment Strategies

As the evidence was deemed insufficient to compare siponimod to alternative DMTs, the base case comparator evaluated in this model was BSC.

- Siponimod (Novartis)
- Best supportive care

Key Model Characteristics and Assumptions

Below is a list of key model choices:

- Cycle length of one year
- Lifetime horizon
- Transitions based on SPMS natural history data from the London, Ontario cohort[42,108]
- Efficacy of siponimod based on the relative risk of disability progression and relative risk of relapse from the EXPAND trial compared to placebo
- Inclusion of direct health care costs for each EDSS health state based on published literature
- 3% discount rate applied to costs and outcomes
- No stopping rule associated with EDSS score applied to the overall SPMS population
- Stopping rule at EDSS 7 for active SPMS

Table 4.2. Key Model Assumptions

Assumption	Rationale
For the overall SPMS population, patients receiving siponimod therapy who progress on treatment continue treatment (aside from an overarching rate of discontinuation per cycle). Active SPMS patients discontinue siponimod at EDSS 7, when the rate of relapse begins to decline.	Based on expert clinician input that no best practices currently exist to inform when to stop siponimod in patients with SPMS. For active disease, discontinuation assumed at EDSS 7, when the rate of relapse begins to decline as an indicator for when disease becomes non-active.
Patients who discontinue siponimod follow the natural history progression of disease.	No evidence exists to model extended treatment benefit with siponimod after a patient has discontinued.
Patients who discontinue siponimod receive no additional DMT.	Efficacy of additional treatment after discontinuation of siponimod is unknown.
The relative risk of progression observed in the siponimod clinical trials vs. placebo is applied to natural history transition probabilities to calculate a new set of transition probabilities for siponimod. The relative risk observed during the trial is extrapolated for the entire duration a patient is receiving treatment.	No loss of response was observed from the primary timepoint of 3 months to a secondary analysis at 6 months. Therefore, patients were assumed to receive treatment benefit while on treatment.
Mortality is calculated using US life-tables and applying a relative risk of mortality based on EDSS health state. Treatments have an indirect effect on mortality by delaying time to advanced EDSS states, where risk of mortality is higher.	No mortality benefit was observed in the siponimod trial; however, significantly increased risk of mortality has been demonstrated for increasing MS severity.
The annual rate of discontinuation is based on the reported data in the EXPAND trial for the first 2 years (9.4% for years 1 and 2), then a lower rate thereafter (3% in years 3 and beyond).	At present, no data exist to inform real-world treatment patterns associated with siponimod. As such, the model mirrors the annualized discontinuation rate observed in the EXPAND trial for years 1 and 2. Real-world discontinuation patterns may be reflected by a lower long-term discontinuation rate.
Cost and disutility associated with a relapse in SPMS are similar to those with RRMS.	No evidence exists to inform relapse cost and disutility specifically for patients with SMPS.
Health state utility in the EDSS 9 state is zero.	The base-case source of utility values for SPMS had inadequate sample size to estimate utility for EDSS 9. Even though alternative sources have found negative utility values for this health state, in the absence of data from the primary source, we assumed a utility of zero.

Model Inputs

Clinical Inputs

Treatment efficacy is included in the model in two ways: 1) risk of disability progression to higher EDSS state, and 2) relative risk of relapse (Table 4.3),[19] with these inputs acquired from the EXPAND trial.

Table 4.3. Key Model Inputs

	Hazard Ratio for Disability Progression (95% CI)	Relative Risk for Relapse (95% CI)	Primary Source
Overall SPMS Population	0.79 (0.65 to 0.95)*	0.45 (0.34 to 0.59)	Kappos 2018
Patients With Relapses Within 2 Years of Enrollment (Active SPMS)	0.67 (0.49 to 0.91)	0.45 (0.34 to 0.59)	Kappos 2018
Patients Without Relapses Within 2 Years of Enrollment (Non-active SPMS)	0.87 (0.68 to 1.11)	0.45 (0.34 to 0.59)	Kappos 2018

*Primary endpoint of confirmed disability progression at three months. Secondary endpoint of confirmed disability progression at six months will also be considered in sensitivity analysis (HR 0.74 [0.60 to 0.92]).[19]

Clinical Probabilities/Response to Treatment

The transitions between EDSS states in the absence of DMT will be based on data from the London, Ontario cohort.[42,108]

Table 4.4. Natural History Annual Transition Probabilities for SPMS[6,23]

		EDSS State at End of Year								
		1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
EDSS State at Start of Year	**1**	0.769	0.154	0.077	0.000	0.000	0.000	0.000	0.000	0.000
	2	-	0.636	0.271	0.062	0.023	0.008	0.000	0.000	0.000
	3	-	-	0.629	0.253	0.077	0.033	0.003	0.005	0.000
	4	-	-	-	0.486	0.350	0.139	0.007	0.018	0.000
	5	-	-	-	-	0.633	0.317	0.022	0.026	0.002
	6	-	-	-	-	-	0.763	0.190	0.045	0.002
	7	-	-	-	-	-	-	0.805	0.189	0.006
	8	-	-	-	-	-	-	-	0.926	0.074
	9									1.000

The natural history transition matrix presented in Table 4.4 was used to calculate transition probabilities using siponimod for SPMS by applying the hazard ratio for confirmed disability progression in Table 4.3. Adjusted transition probabilities for siponimod are presented in Table 4.5 and were calculated using the formula: $1-(1-p)^{HR}$ where p is the natural history transition probability and HR is the hazard ratio for disability progression.

Table 4.5. Annual Transition Probabilities Using Siponimod for SPMS

Overall SPMS Population

		EDSS State at End of Year								
		1	2	3	4	5	6	7	8	9
EDSS State at Start of Year	1	0.815	0.124	0.061	0.000	0.000	0.000	0.000	0.000	0.000
	2	-	0.705	0.221	0.049	0.018	0.006	0.000	0.000	0.000
	3	-	-	0.700	0.206	0.061	0.026	0.002	0.004	0.000
	4	-	-	-	0.580	0.288	0.112	0.006	0.014	0.000
	5	-	-	-	-	0.700	0.260	0.017	0.021	0.002
	6	-	-	-	-	-	0.809	0.153	0.036	0.002
	7	-	-	-	-	-	-	0.843	0.153	0.005
	8	-	-	-	-	-	-	-	0.941	0.059
	9									1.000

Active SPMS Population

		EDSS State at End of Year								
		1	2	3	4	5	6	7	8	9
EDSS State at Start of Year	1	0.842	0.106	0.052	0.000	0.000	0.000	0.000	0.000	0.000
	2	-	0.746	0.191	0.042	0.015	0.005	0.000	0.000	0.000
	3	-	-	0.743	0.178	0.052	0.022	0.002	0.003	0.000
	4	-	-	-	0.637	0.251	0.095	0.005	0.012	0.000
	5	-	-	-	-	0.741	0.225	0.015	0.017	0.001
	6	-	-	-	-	-	0.837	0.132	0.030	0.001
	7	-	-	-	-	-	-	0.805	0.189	0.006
	8	-	-	-	-	-	-	-	0.926	0.074
	9									1.000

The mean annual relapse rates by EDSS state are presented in Table 4.6.[41,42,109] In the EXPAND trial, the mean (SD) number of relapses in the year before screening was 0.2 (0.5) in the siponimod arm and 0.3 (0.6) in the placebo arm.[19] Relapse rates by EDSS health state were not available from the EXPAND trial. Literature-based estimates for relapse rates in SPMS present higher relapse rates than observed in the baseline patient characteristics of the EXPAND trial. For the base case overall SPMS population, we used relapse rates by EDSS health state based on a 1982 study by Patzold and Pocklington.[109] In subsequent cost-effectiveness studies, these observed rates have been adjusted upwards to reflect relapse rates observed in the clinical trials of drugs to treat RRMS.[41,42] With the approved labeling for siponimod reflecting a population with active disease, relapse rates for active SPMS patients treated with siponimod are expected to be higher than those for the overall SPMS population enrolled in the EXPAND trial. For this reason, the adjusted relapse rates based on Bozkaya 2017 were used for the active SPMS subgroup analysis. For the scenario analysis of the subgroup of patients with no relapses in the two years prior to study enrollment, i.e. patients with non-active SPMS, the rates of relapse for all EDSS scores were assumed to be zero to model a population which no longer is experiencing MS relapses.

Table 4.6. Mean Relapse Rates Per Year by EDSS State

EDSS State	Relapse Rate (Overall SPMS)[42,109]	Relapse Rate (Active SPMS)[41]	Relapse Rate (Non-active SPMS) (Scenario Analysis)[42]
1	0.00	0.00	0.00
2	0.47	0.91	0.00
3	0.88	1.64	0.00
4	0.55	1.05	0.00
5	0.52	1.27	0.00
6	0.45	1.10	0.00
7	0.34	0.82	0.00
8	0.34	0.82	0.00
9	0.34	0.82	0.00

In accordance with the previous ICER evaluation in MS, we assumed that 70.8% of relapses are mild or moderate and 29.2% are severe.[45,110]

Mortality

Background mortality rates were based on age- and sex-specific US life tables using the Human Mortality database's US-specific tables,[111] adjusted for MS-specific mortality using an EDSS-specific mortality multiplier.[44,111] Multiple sets of mortality multipliers are available in the data for patients with MS by EDSS health state.[44,112] Recently, Harding et al. presented updated mortality multipliers for EDSS health states above EDSS 4 based on an MS registry in southeast Wales. These findings are much higher than previous estimates, especially for EDSS 8 and 9, with increased mortality 60 times higher than the general population.[112] These estimates were considered to be unrealistic and inconsistent with previous publications that reported a relatively small impact of MS on life expectancy; some models even excluded mortality adjustment entirely.[93,94,96,106]

For the base-case evaluation, the mortality multipliers used were based on Pokorski (1997), with a sensitivity analysis for EDSS score 4 and above based on values from Harding 2018 (Table 4.7).[44,112]

Table 4.7. Calculated Mortality Multipliers of All-Cause General Population Mortality, by EDSS State, to be Applied to Age-Specific Mortality Rates

EDSS State	Linear Interpolation from Pokorski 1997*[44] (Base Case)	Harding 2018 (95% CI)[112] (Sensitivity Analysis)
1	1.43	-
2	1.60	-
3	1.64	-
4	1.67	2.02 (0.98 - 3.71)
5	1.84	2.02 (0.98 - 3.71)
6	2.27	3.86 (2.63 - 5.47)
7	3.10	4.76 (2.82 - 7.56)
8	4.45	22.17 (18.20 - 26.75)
9	6.45	60.74 (47.62 - 76.41)
Previous Models Using These Inputs	41,42,45,95,103,105,113	None due to recent publication of these data

Utilities

Total utility each year was calculated as utility based on EDSS health state minus disutility associated with relapses. Multiple sources exist to inform utility values by EDSS health state for patients with SPMS, which are presented in Table 4.8. The EDSS health state utility values based on Hawton (2016) will be used as the base-case analysis, as these provide recent estimates of utility values for SPMS.[114] For health states without a utility value specific to SPMS (EDSS 1-5), the overall MS health state utility value was used. For EDSS 9, we assumed a utility of zero. A sensitivity analysis was conducted using alternative utility values from Orme (2007).[43]

Table 4.8. Utility Values for Health States

EDSS State	Hawton 2016[114] (EQ-5D) (Base Case)	Orme 2007[43] (EQ-5D) (Sensitivity Analysis)
1	0.762 ± 0.220*	0.754
2	0.711 ± 0.221*	0.660
3	0.608 ± 0.281*	0.528
4	0.609 ± 0.256*	0.565
5	0.531 ± 0.286*	0.473
6	0.481 ± 0.269	0.413
7	0.397 ± 0.317	0.252
8	0.021 ± 0.387	-0.094
9	0	

*Value for all MS diagnoses (not specific to SPMS).

Relapses are associated with a QALY loss of 0.091 per cycle with a mild/moderate relapse and 0.302 per cycle with a severe relapse.[45,46]

The impact of SPMS on caregivers is an important consideration to capture for treatments which aim to reduce disability and is included as a separate scenario analysis. The disutility experienced by caregivers who support patients with MS has been modeled previously.[95,103,105,113] Nearly half (43%) of the survey participants in the observational study by Acaster et al. cared for patients with SPMS, and their responses were used for caregiver disutility.[115] The findings suggest that caregiver disutility is impacted earlier than was found in previous estimates.[95,103,113,116]

Table 4.9. Caregiver Disutility by Health State

EDSS State	Caregiver Disutility (Base Case) (Acaster 2013)[115]
1	-0.002
2	-0.002
3	-0.002
4	-0.045
5	-0.142
6	-0.167
7	-0.063
8	-0.095
9	-0.095

Adverse Events

Based on the EXPAND trial, adverse events associated with siponimod were mild and similar to best supportive care and were therefore not considered in the model.

Economic Inputs

Drug Acquisition Costs

In the absence of an estimated net price for siponimod, the price of siponimod used in the model was based on the wholesale acquisition cost (WAC).[47] The average discount applied to interferon beta-1b was derived using data from SSR Health that combined data on net US dollar sales with information on unit sales to derive net pricing at the unit level across all payer types.[117] We also calculated the threshold prices at three willingness to pay (WTP) thresholds: $50,000, $100,000, and $150,000 per QALY gained.

Table 4.10. Drug Cost Inputs

Drug Name, Labeled Dose, Administration Route	Strength	WAC[47]	Net Price	Acquisition Cost per Year
Siponimod (Mayzent), 1 mg daily, oral	0.25 mg	$1,697.26/28 EA	TBD	$88,561
Siponimod (Mayzent), 2 mg daily, oral	2 mg	$7,273.97/30 EA	TBD	$88,561
Interferon beta-1b (Betaseron), 250 µg, every other day, subcutaneous	250 µg	$7,596.85/14EA	$4,119.90	$53,741
Best supportive care	N/A	$0	$0	$0

EA: each, N/A: not applicable

Siponimod is an oral agent with once daily dosing.[19] In the absence of real-world data on adherence, the model assumes that patients are fully adherent (i.e., receive once daily dosing for 12 months per year) while still receiving treatment (i.e., not discontinued). The recommended dose per day of siponimod (in mg) may depend on a patient's CYP2C9 metabolic rate, determined during initial screening. The recommended maintenance dose of siponimod is 2 mg per day for approximately 90% of patients with regular siponimod metabolism and 1 mg per day for the 10% of patients with intermediate siponimod metabolism. Patients with poor siponimod metabolism are assumed to be ineligible for treatment. Patients receiving best supportive care do not incur SPMS-specific drug treatment costs.

Administration and Monitoring Costs

As siponimod is orally administered, no costs are associated with siponimod administration in the model. All patients initiating siponimod will be subject to genetic screening to identify CYP2C9 metabolic function, at a cost of $174.81 per patient (HCPCS 81227).[118] Based on the patients who qualified for expanded cardiac monitoring in the EXPAND trial, 30% of patients may require cardiac monitoring for the first dose of siponimod.[19] The monitoring protocol for these patients is assumed to be similar to that for fingolimod in the 2017 ICER evaluation of DMTs for RRMS and PPMS, which consists of observing patients for bradycardia for at least 6 hours, monitoring pulse and blood pressure hourly, as well as electrocardiograms (ECGs) prior to dosing and at the end of the observation period, with a cost of two electrocardiograms, CPT 93000 ($17.28) and one specialist visit, CPT 99215 ($147.76).[119]

Interferon beta-1b is self-administered subcutaneously every other day, with no direct cost attributable to administration. Complete blood and differential white blood cell counts, platelet counts and blood chemistries, including liver function tests, are recommended at regular intervals (one, three, and six months) following introduction of therapy, and then periodically thereafter in the absence of clinical symptoms (assumed to be twice per year).[29]

Table 4.11. Monitoring Costs

	First Year						Subsequent Years (per Year)		
	CBC	CYP2C9	ECG	LFT	MRI	Office Visit	CBC	LFT	MRI
Unit Cost	$9.59	$174.81	$17.28	$10.09	$411.84	$147.76	$9.59	$10.09	$411.84
Utilization									
Siponimod	0	1	2*	0	0	1*	0	0	0
Interferon Beta-1b	3	0	0	3	0	0	2	2	0
Best Supportive Care	0	0	0	0	0	0	0	0	0

*Among the 30% of patients with need for expanded cardiac monitoring

CBC: complete blood count, CYP2C9: Cytochrome P450 2C9, ECG: electrocardiogram, LFT: liver function tests, MRI: magnetic resonance imaging

Health Care Utilization Costs

Direct health care costs were calculated based on previously published cost data for each EDSS health state, as done for the previous ICER evaluation of DMT for RRMS (Table 4.12).[45,46,120] Relapses incur a mean annual direct cost of $2,747 per relapse (both mild/moderate and severe) (inflated to $3,064 2018 US dollars).[46] All costs in Table 4.12 are inflated to 2018 US dollars using the Personal Health Care (PHC) Expenditure deflator up to 2017 and then the personal consumption expenditure (PCE) price index to update to 2018.

Table 4.12. Mean Annual Direct Health Care Costs by Health State (2018 USD)

EDSS State	Direct Health Care Costs
1	$5,123
2	$7,266
3	$9,408
4	$11,551
5	$13,694
6	$15,836
7	$17,979
8	$20,121
9	$22,264

Extrapolated from Kobelt 2006, Figure 2 for direct costs + other drugs using equation: Cost = 1594.1*EDSS + 2217.5 in 2004 US dollars, inflated to 2018 US dollars.

Productivity Costs

Indirect costs were calculated based on previously published cost data for each EDSS health state, as done for the previous ICER evaluation of DMTs for RRMS (Table 4.13).[20,37] Indirect costs for productivity include short-term absence from work, reduced working time, and early retirement.

Relapses incur an additional mean indirect cost of $2,423 per relapse (inflated to $2,702 2018 US dollars).[46]

Table 4.13. Mean Annual Indirect Health Care Costs by Health State (2018 USD)

EDSS State	Indirect Costs
1	$15,460
2	$19,619
3	$23,778
4	$27,938
5	$32,097
6	$36,256
7	$40,415
8	$44,575
9	$48,734

Extrapolated from Kobelt 2006, Figure 2 for informal care + indirect costs using equation: Cost = 3094.5*EDSS + 8407.5.

Sensitivity Analyses

We ran one-way sensitivity analyses to identify the key drivers of model outcomes, using available measures of parameter uncertainty (i.e., standard errors) or reasonable ranges for each input described in the model inputs section above. Probabilistic sensitivity analyses were also performed by jointly varying all model parameters over 5,000 simulations, then calculating 95% credible range estimates for each model outcome based on the results. We used normal distributions for costs, rates, multipliers, and ages; log-normal for relative risks; gamma distributions for negative utilities; and beta distributions for probabilities and utilities. Additionally, we performed a threshold analysis by systematically altering the price of siponimod to estimate the maximum prices that would correspond to given willingness to pay (WTP) thresholds for both of the populations of interest (the overall SPMS clinical trial population and subgroup with active SPMS).

Scenario Analyses

A list of the scenario analyses conducted are presented in Table 4.14.

Table 4.14. List of Scenario Analyses

Scenario Analyses
Interferon beta-1b as comparator using MAIC
Modified societal perspective including indirect costs
Inclusion of caregiver burden
Discontinuation of siponimod at EDSS 8 or 9 in the subpopulation with active SPMS
Relative risk of disability progression for siponimod based on 6-month timepoint of the EXPAND trial
Utility values based on Orme 2007
Mortality multipliers by EDSS score from Harding 2018 for EDSS scores 4-9
Subpopulation with non-active SPMS

Model Validation

We used several approaches to validate the model. First, we varied model input parameters to evaluate face validity of changes in results. We performed model verification for model calculations using internal reviewers. Second, we compared our model and results to other cost-effectiveness models in this therapy area. We provided preliminary methods and results to manufacturers, patient groups, and clinical experts, and received feedback on those. Finally, we provided manufacturers the opportunity to review and provide comments on the model via a licensing arrangement.

4.3 Results

Base Case Results

Total discounted costs, life-years, life-years with ambulation, and QALYs over the lifetime horizon are shown in Table 4.15. Undiscounted results are presented in Appendix Table E2. Among patients with SPMS, discounted costs for MS-related health care (excluding drug costs) over the projected lifetime were approximately $276,000 for siponimod and $283,000 for BSC. Discounted life expectancy from age of initiation (age 48 years) was 14.6 years for siponimod and 14.4 years for BSC. The discounted number of life years in an ambulatory state was 5.16 years for siponimod and 4.45 years for BSC. Finally, projected discounted QALYs were 3.41 for siponimod and 2.66 for BSC.

Among patients with active SPMS, projected discounted MS-related health care costs were slightly higher for BSC and siponimod relative to the overall SPMS population due to the increased rate of relapses ($307,000 for BSC and $297,000 for siponimod). Life-years (14.4) and life-years in an ambulatory state (4.45) were identical to the overall SPMS population for BSC but QALYs were lower (1.48) due to the disutility associated with a greater rate of relapses in the subgroup with active SPMS. Life-years, ambulatory life-years, and QALYs for siponimod were 14.7 years, 5.69 ambulatory years, and 2.42 QALYs.

Table 4.15. Discounted Results for the Base Case for Siponimod Compared to BSC

Regimen	Drug Cost	Other Direct Costs	LYs	Ambulatory LYs	QALYs
Overall SPMS Population					
Siponimod	$872,000	$276,000	14.6	5.16	3.41
BSC	$0	$283,000	14.4	4.45	2.66
Active SPMS Population					
Siponimod	$416,000	$297,000	14.7	5.69	2.42
BSC	$0	$307,000	14.4	4.45	1.48

Costs rounded to the nearest thousand.
LY: life year, QALY: quality-adjusted life year, SPMS: secondary progressive multiple sclerosis

In the overall SPMS population, siponimod had a cost per additional life year of approximately $3.76 million, cost per ambulatory life year of approximately $1.22 million, and cost per additional QALY of approximately $1.15 million, compared to BSC. These higher figures are reflective, in part, of the large differences in projected cost between siponimod and BSC (Table 4.16).

The cost effectiveness of siponimod in the subgroup of patients with relapses within 2 years of enrollment, i.e., patients with active SPMS, is more favorable than in the overall population, with a cost per additional life year of approximately $1.57 million, cost per additional year of ambulation of $329,000, and cost per additional QALY of $433,000. This result is influenced by the greater reduction in the risk of disability progression and the stopping rule used in this subgroup compared to the overall SPMS population.

Table 4.16. Pairwise Results for Siponimod Compared to BSC

Regimen	Cost per Additional Life Year	Cost per Life Year of Ambulation	Cost per Additional QALY
Overall SPMS Population			
Siponimod	$3,760,000	$1,220,000	$1,150,000
Active SPMS Population			
Siponimod	$1,565,024	$329,000	$433,000

Results rounded to nearest ten thousand (overall), thousand (active).
QALY: quality-adjusted life year.

The annual cost of siponimod that would achieve cost-effectiveness thresholds of $50,000, $100,000, and $150,000 per QALY gained in the overall SPMS and active SPMS subpopulation are presented in Table 4.17.

Table 4.17. Annual Threshold Pricing for the Base Case (Overall and Active SMPS Population)

Drug	Base-Case Cost	$50,000/QALY	$100,000/QALY	$150,000/QALY
Overall SPMS Population				
Siponimod	$88,561	$4,529	$8,364	$12,199
Active SPMS Population				
Siponimod	$88,561	$11,980	$21,988	$31,996

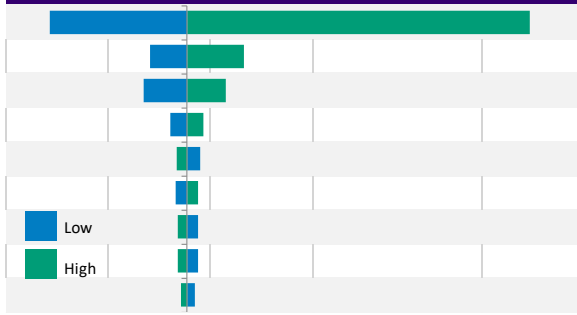
QALY: quality-adjusted life year

Sensitivity Analysis Results – One Way

To demonstrate effects of uncertainty on both costs and health outcomes, we varied input parameters across the 95% CI (if available) or ± 10% to evaluate changes in the cost per additional QALY for siponimod compared to best supportive care. For the overall SPMS population and subpopulation with active SPMS, the hazard ratio for time to disability progression was the most influential driver of model results. For the overall SPMS population and subpopulation with active disease, the relative risk of relapse, followed by the price of siponimod, were the second and third most impactful, respectively.

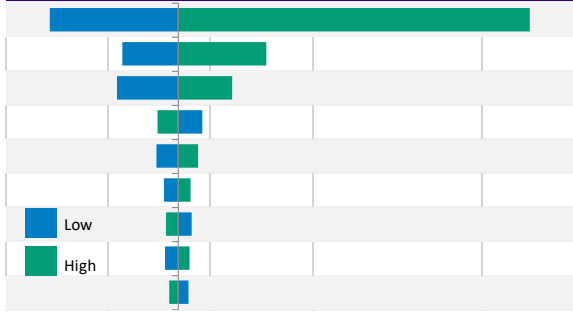
Figure 4.2. One-Way Sensitivity Analysis: Cost Per Additional QALY for Siponimod Compared to Best Supportive Care for SPMS

Overall SPMS Population



Parameter	Base case	Low Value	High Value	Low Result	High Result	Δ
HR of progression for siponimod	0.79	0.65	0.95	$784,991	$2,047,303	$1,262,312
Relapse RR for siponimod	0.45	0.34	0.59	$1,049,555	$1,295,825	$246,270
Siponimod list price per 30 days	$7,274	$6,547	$8,001	$1,030,066	$1,248,307	$218,240
Proportion of relapses which are mild/moderate	70.8%	63.7%	77.9%	$1,101,509	$1,187,794	$86,285
Utility for EDSS 6	0.481	0.433	0.529	$1,179,342	$1,117,042	$62,301
Discount rate for outcomes	3.0%	2.7%	3.3%	$1,114,697	$1,173,279	$58,582
Discount rate for costs	3.0%	2.7%	3.3%	$1,174,913	$1,120,473	$54,440
Annual utility decrement of severe relapse	0.302	0.272	0.332	$1,173,221	$1,121,977	$51,244
Annual utility decrement of mild/moderate relapse	0.091	0.082	0.100	$1,165,632	$1,128,228	$37,404

Active SPMS Population



Parameter	Base case	Low Value	High Value	Low Result	High Result	Δ
HR of progression for siponimod	0.67	0.49	0.91	$339,727	$688,697	$348,970
Relapse RR for siponimod	0.45	0.34	0.59	$392,318	$497,069	$104,751
Siponimod list price per 30 days	$7,274	$6,547	$8,001	$388,410	$472,058	$83,649
Utility for EDSS 6	0.481	0.433	0.529	$450,570	$417,892	$32,678
Proportion of relapses which are mild/moderate	70.8%	63.7%	77.9%	$417,012	$447,626	$30,613
Mean age at baseline (years)	48.0	43.2	52.8	$422,337	$442,241	$19,904
Annual utility decrement of severe relapse	0.302	0.272	0.332	$442,475	$424,300	$18,175
Discount rate for outcomes	3.0%	2.7%	3.3%	$423,308	$441,045	$17,737
Annual relapse rate for EDSS 6	1.100	0.990	1.210	$440,174	$426,192	$13,982

EDSS: Expanded Disability Status Scale, HR: hazard ratio, QALY: quality-adjusted life year, RR: relative risk, SPMS: secondary progressive multiple sclerosis

Sensitivity Analysis Results – Probabilistic

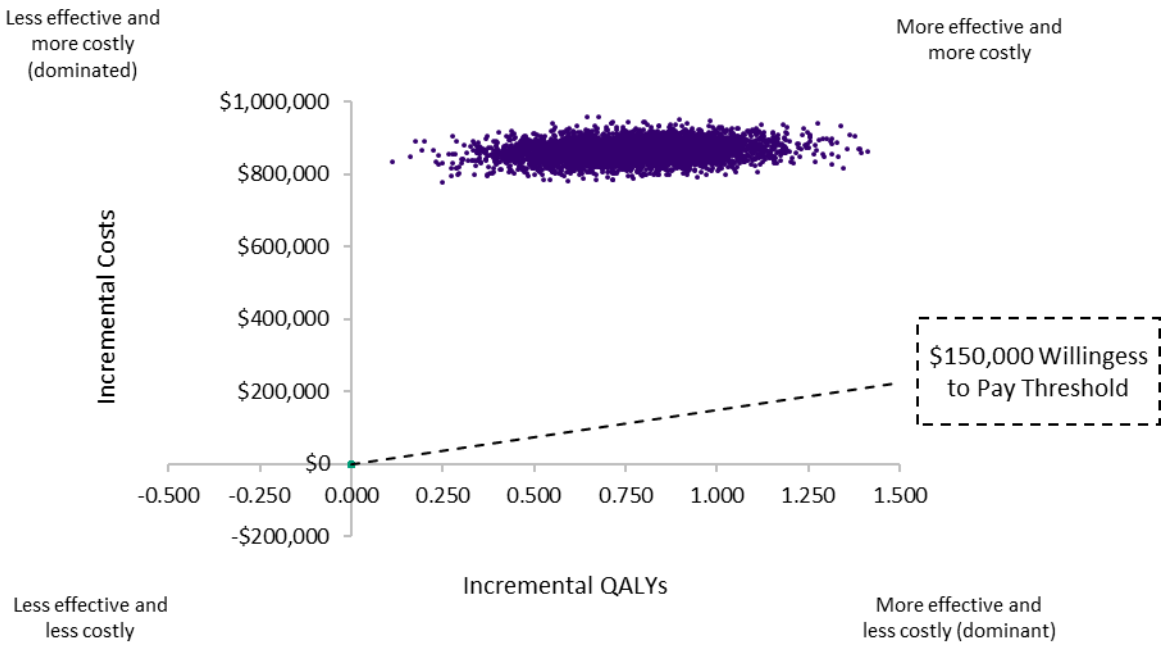
The results of our probabilistic sensitivity analysis show wide variability in the cost per additional QALY for siponimod compared to BSC. Out of 5,000 model iterations for each population, none had an additional cost per QALY result below the threshold of $150,000 for the overall SPMS population or for the subgroup with active SPMS (Appendix Figure E1). Mean and 95% credible interval values for probabilistic sensitivity analyses of siponimod compared to BSC in the overall SPMS population are shown in Table 4.18. The results of probabilistic sensitivity analyses suggest a large degree of uncertainty in the model parameters that impact QALYs. Results were unlikely to yield a cost per additional QALY for siponimod compared to BSC that would fall below commonly accepted thresholds for the overall SPMS population or subgroup with active SPMS based on the current list price for siponimod.

Table 4.18. Pairwise Results of Probabilistic Sensitivity Analysis for Siponimod Compared to BSC

Treatment	Cost per Additional Life Year Mean (Credible Range)	Cost per Life Year of Ambulation Mean (Credible Range)	Cost per Additional QALY Mean (Credible Range)
Overall Population	$3,630,000 ($2,150,000–$14,950,000)	$1,170,000 ($683,000–$4,870,000)	$1,120,000 ($811,000–$1,950,000)
Active SPMS Population	$1,470,000 ($962,000–$4,690,000)	$311,000 ($211,000–$961,000)	$419,000 ($334,000–$658,000)

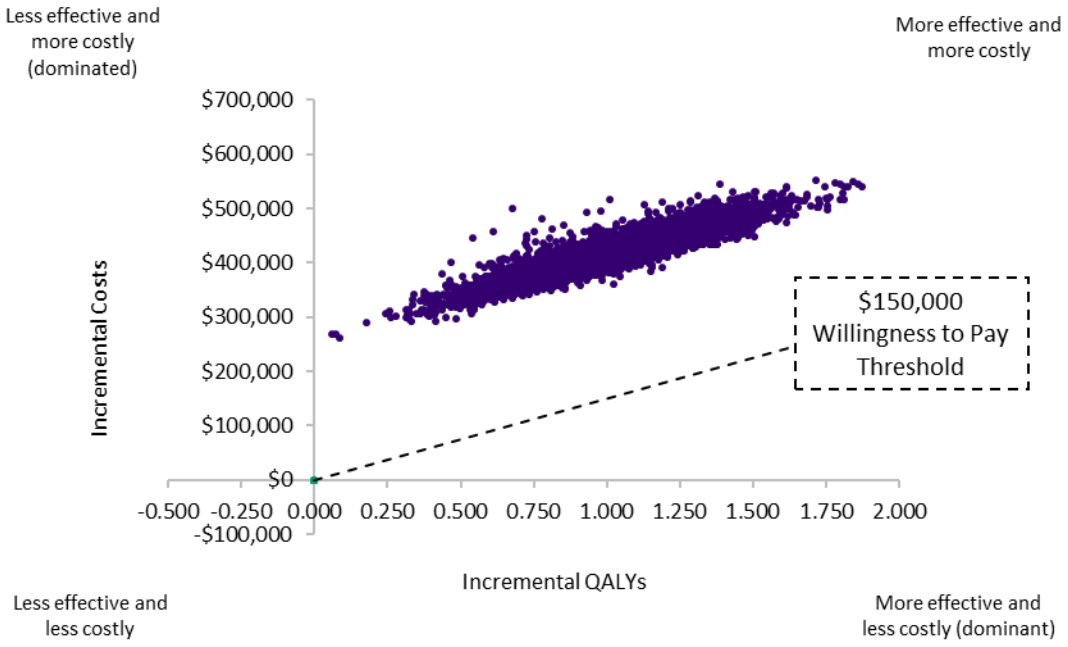
BSC: best supportive care, QALY: quality-adjusted life year

Figure 4.3. Probabilistic Sensitivity Analysis: Incremental Cost-Effectiveness Plane for Cost per Additional QALY for Siponimod Compared to BSC for Overall SPMS Population



BSC: best supportive care, QALY: quality-adjusted life year, SPMS: secondary progressive multiple sclerosis, WTP: willingness-to-pay.

Figure 4.4. Probabilistic Sensitivity Analysis: Incremental Cost-Effectiveness Plane for Cost per Additional QALY for Siponimod Compared to BSC for Active SPMS



BSC: best supportive care, QALY: quality-adjusted life year, SPMS: secondary progressive multiple sclerosis, WTP: willingness-to-pay.

Scenario Analyses Results

Multiple scenarios were explored, varying sources of inputs and key assumptions of the model. Some alternative scenarios resulted in lower costs and improved outcomes compared to the base case. However, incremental cost per QALY remained well above $150,000 per life year, per life year of ambulation, and per QALY. Results of scenarios are listed in Appendix Table E3. A description of selected scenario analyses is presented below.

Alternative DMTs as Comparators Using MAIC Analysis

The manufacturer of siponimod, Novartis, submitted an academic-in-confidence matching-adjusted indirect comparison (MAIC) comparing siponimod to other DMTs that have been evaluated in SPMS. These included interferon beta-1b (North American study and European study), interferon beta-1a (Nordic SPMS study, SPECTRIMS study, IMPACT study), and natalizumab (ASCEND trial).[21,22,24-26,30] This type of analysis seeks to provide comparative evidence when no direct evidence is available and more traditional evidence synthesis methods are not considered possible or valid. The MAIC matches patient-level data from the EXPAND trial with aggregate data from individual trials of the comparator therapies according to inclusion and exclusion criteria, and then adjusts for potential treatment effect modifiers.

The submitted MAIC appears to be well conducted but was of limited use in this report due to limitations inherent to the MAIC and limitations of the individual comparator trials including inconsistencies in endpoints, clinically relevant dosing, and the inability to fully adjust for potential effect modifiers. In addition, clinical guidelines recommend that clinicians consider discontinuation of a DMT in patients with non-relapsing, progressive MS and most of the interferon trials included in the MAIC had greater than 50% of patients with non-relapsing forms of the disease.[73,121] One trial comparing interferon beta-1b to placebo in a European cohort, however, had a high proportion of patients (approximately 70%) with the relapsing form of the disease. We have therefore included a scenario comparing siponimod to interferon beta-1b based on this study, as it is the most similar to the indicated population for the beta interferons and siponimod. We did not include a comparison with natalizumab due to the proportion of the trial population that had non-relapsing disease (71%) as well as differences in the way the primary endpoints were calculated for the siponimod and natalizumab trials.[30] Ocrelizumab was not able to be included in the MAIC. The MAIC data we used will be unredacted within the next 18 months per ICER's confidential data policy.

Interferon beta-1b as a Comparator

The cost-effectiveness of siponimod over interferon beta-1b was evaluated against the European trial of interferon beta-1b[21] using the 3-month hazard ratio of disability progression. Patients enrolled in the European trial reflected an SPMS population with relatively more active disease,

with 70% experiencing relapse in the 2 years prior to study. In this study, interferon beta-1b demonstrated a statistically significant benefit versus placebo for time to confirmed disability progression at 3 months in patients with SPMS (HR 0.74, 95% CI 0.60-0.91).[122] The MAIC adjusted for differences in age, EDSS, and the proportion of patients relapse-free in two years prior to study. Under this scenario, the hazard ratio for siponimod versus interferon beta-1b was applied to the hazard ratio of progression for interferon beta-1b versus placebo to calculate a transition probability matrix for siponimod. As a net price for siponimod was not available at the time of analysis, list price for siponimod ($7,273.97) was compared against the net price for interferon beta-1b ($4,119.90).

Results of this scenario, comparing the siponimod to interferon beta-1b, were less favorable than the base case of siponimod compared to BSC. Comparing siponimod to interferon beta-1b using the MAIC analysis produced results of $4.83 million per life-year gained, $1.37 million per ambulatory life-year gained, and $2.11 million per QALY gained for siponimod vs interferon beta-1b (Table 4.19). These represent conservative estimates, as contractual discounts on the list price for siponimod would result in more favorable cost-effectiveness results for siponimod vs interferon beta-1b. A discount of approximately 31% off the list price of siponimod would be required to meet the $150,000/QALY threshold versus interferon beta-1b in this scenario.

Table 4.19. Pairwise Results for Siponimod Compared to Interferon Beta-1b

Interferon Beta-1b European Trial as Comparator	Cost per Additional Life Year	Cost per Life Year of Ambulation	Cost per Additional QALY
European Trial			
Siponimod	$4,830,000	$1,370,000	$2,110,000

Modified Societal Perspective

In the modified societal perspective scenario, we included indirect costs, i.e., productivity costs. This increased the projected costs for siponimod and BSC without changing health outcomes from the base case. This resulted in quantitative but non-influential changes from the base case at $3.73 million per life year gained, $1.21 million per ambulatory life year gained, and $1.14 per QALY gained.

Model Validation

Model validation followed standard practices in the field. We tested all mathematical functions in the model to ensure they were consistent with the report. We also conducted sensitivity analyses with extreme input values to ensure the model was producing findings consistent with expectations. Further, independent modelers tested the mathematical functions in the model as well as the specific inputs and corresponding outputs.

Model validation was also conducted in terms of comparisons to other model findings. We searched the literature to identify models that were similar to our analysis, with comparable populations, settings, perspective, and treatments.

Prior Economic Models

We searched the literature to identify models that were similar to our analysis, with comparable populations, settings and perspective. Because siponimod was a new treatment, we found no models comparing siponimod to other treatment options in patients with SPMS. Given that SPMS could also be a component of RRMS disease models,[41,94,104,123,124] we limited our search to the SPMS-specific models evaluating DMTs used in SPMS patients.

Touchette et al.[91] examined the cost utility of intravenous mitoxantrone hydrochloride administered every 3 months, interferon beta-1b administered every other day, and routine supportive care. The model was a Markov model based on EDSS scores, using both a US insurer and a societal perspective (including direct health care and total costs, respectively). All patients were at EDSS score of 3 at baseline as opposed to the EDSS distribution in our model. Time horizon was 10 years whereas it was life-time in our analysis. Mitoxantrone compared to supportive care was estimated to cost approximately $58,000 (2003 US$) per QALY from the insurer's perspective and to be cost-saving from the societal perspective; interferon beta-1b versus supportive care was not likely to meet conventional cost-effectiveness thresholds, at approximately $741,000 (2003 US$) and $658,000 (2003 US$) per QALY from the insurer's and society's perspectives, respectively. Over a 10 year-time horizon using a 5% discount rate, mitoxantrone and interferon beta 1-b resulted with 5.09 and 5.17 QALYs gained compared to supportive care, respectively.

Forbes et al.[92] evaluated the cost-utility of interferon beta-1b against best supportive care in SPMS patients from the UK health care perspective for a 3-year time horizon. They found that under UK settings the cost per QALY gained from interferon beta was approximately $1,464,000 (1999 US$) due to the high drug cost and modest clinical effect. Compared to supportive care, Interferon beta-1b provided 0.40 QALYs gained over 30 months (using a discount rate of 6%).

Kobelt et al.[93] estimated the cost effectiveness of interferon beta-1b versus placebo in SPMS patients using a Markov model with states based on disability expressed by EDSS scores. Because the trial was for 3 years, the natural course of the disease was extrapolated up to 10 years by using the placebo group in the trial. The study took a Swedish societal perspective and the time horizon was 10 years. The estimated incremental cost per QALY was approximately $39,000 (2000 US$) when all costs (direct, informal care, and indirect) are included. When indirect costs were excluded, the cost per QALY was approximately $62,000 (2000 US$).

As a follow-up to the aforementioned Kobelt et al. study, another analysis by Kobelt et al.[90] repeated the same analysis by using a geographically-based epidemiologic study of the natural

history of MS in Canada for the data extrapolation up to 10 years. They found that long-term progression of disability, and accordingly, the potential treatment benefit, were underestimated using this method. Using the epidemiologic data, the estimated incremental cost per QALY was $25,700 (2002 US$), when all costs (direct, informal care, and indirect) were included. The lower cost-effectiveness ratio was mostly due to a larger QALY gain with treatment than in the previous model. The resulting QALY gain over 10 years was 0.217 (discounted 3%) compared with 0.162 in the previous model.[93]

Note that the cost per QALY results in both Kobelt et al. studies differ considerably from those of other studies. One major difference is that Kobelt et al. assumed that effects on disease progression and relapses returned to that of placebo after 3 years, the duration of the clinical trial, and that treatment was stopped at the end of the third year. Also, the rapid changes in costs from the early EDSS health states to the advanced EDSS health states, as well as dissimilar utility values obtained through different methodologies, could have contributed to more favorable cost-effectiveness results in the studies by Kobelt et al.[90,93]

Because different time horizons and interventions were examined in these analyses, we could not directly compare the results from our analysis to those from the prior economic models.

4.4 Summary and Comment

We estimated the cost effectiveness of siponimod over a lifetime horizon for all adult patients with SPMS and the subgroup of patients with active SPMS. Patient time spent in EDSS-defined health states was summed to provide estimates of life expectancy and quality-adjusted life expectancy. Annual net health care costs, including drug acquisition, administration, and monitoring costs were summed to estimate lifetime costs for both siponimod and BSC. We used a natural history transition matrix and applied a relative risk for siponimod to derive DMT-specific transition probabilities between EDSS states and also included siponimod's treatment effect on relapse rates and time spent in ambulatory health states. Based on these assumptions, siponimod versus BSC was estimated to cost approximately $1.15 million per QALY gained for the overall SPMS population and $433,000 per QALY for the subgroup population with active SPMS. Based on our analysis the cost per additional QALY for siponimod would exceed commonly-accepted thresholds for cost effectiveness. These results were tested under a variety of assumptions and alternative sources of model inputs, none of which drove the incremental cost per QALY below the threshold of $150,000 per QALY gained.

Limitations

We have attempted to model SPMS treatment to both reflect clinical practice and accommodate the limits of available data. The latter has placed some restrictions on how accurately we can model MS treatment. Natural history data for SPMS patients by EDSS state are from an older study.

The population in this dataset may not represent current MS populations due to differences in diagnostic and treatment practices. The calculation of cost per additional year of ambulation assumes that all patients are wheelchair-bound at EDSS 7 and above and all are ambulatory at EDSS 6 and below.

This analysis is based on the EXPAND trial which enrolled SPMS patients with both active and non-active disease. However, the FDA-approved labeling is limited to SPMS patients with relapsing disease, while also extended to relapsing MS patients in general (not specific to SPMS). In addition, inputs for utility, costs, relapse rates, and efficacy of comparators specific to active SPMS are not available in the literature. For these reasons, our results may not be reflective of the anticipated SPMS patient population in which siponimod is approved and may be used in clinical practice. Lastly, all analyses were based on the list price for siponimod, a higher price than may be paid after contractual negotiations.

Conclusions

In summary, our analyses indicate that siponimod improved health outcomes compared to BSC. Using the current list price for siponimod, results were well above commonly cited thresholds for cost effectiveness for both the overall SPMS trial population and subpopulation with active disease in the base-case analysis and above $150,000 per QALY compared to BSC for all scenarios explored.

5. Potential Other Benefits and Contextual Considerations

Our reviews seek to provide information on potential other benefits offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that would not have been considered as part of the evidence on comparative clinical effectiveness. We also recognize that there may be broader contextual issues related to the severity of the condition, whether other treatments are available, and ethical, legal, or other societal priorities that influence the relative value of illnesses and interventions. These general elements are listed in the table below, and the subsequent text provides detail about the elements that are applicable to the comparison of siponimod to best supportive care. We sought input from stakeholders, including individual patients, patient advocacy organizations, clinicians, and manufacturers, to inform the contents of this section.

Each ICER review culminates in a public meeting of an independent voting Council of clinicians, patients, and health services researchers. As part of their deliberations, Council members will judge whether a treatment may substantially impact the considerations listed in Table 5.1. The presence of substantial other benefits or contextual considerations may shift a council member's vote on an intervention's long-term value for money to a different category than would be indicated by the clinical evidence and cost-effectiveness analyses alone. For example, a council member may initially consider a therapy with an incremental cost-effectiveness ratio of $150,000 per QALY to represent low long-term value for money. However, the Council member may vote for a higher value category if they consider the treatment to bring substantial other benefits or contextual considerations. Conversely, disadvantages associated with a treatment may lead a Council member to vote for a lower value category. A Council member may also determine that there are no other benefits or contextual considerations substantial enough to shift their vote. All factors that are considered in the voting process are outlined in ICER's value assessment framework. The content of these deliberations is described in the last chapter of ICER's Final Evidence Report, which is released after the public meeting.

This section, as well as the Council's deliberation, provides stakeholders with information to inform their decisions on a range of issues, including shared decision-making between patients and clinicians, coverage policy development, and pricing negotiations.

Table 5.1. Potential Other Benefits or Contextual Considerations

Potential Other Benefits
This intervention offers reduced complexity that will significantly improve patient outcomes.
This intervention will reduce important health disparities across racial, ethnic, gender, socio-economic, or regional categories.
This intervention will significantly reduce caregiver or broader family burden.
This intervention offers a novel mechanism of action or approach that will allow successful treatment of many patients for whom other available treatments have failed.
This intervention will have a significant impact on improving return to work and/or overall productivity.
Other important benefits or disadvantages that should have an important role in judgments of the value of this intervention.
Potential Other Contextual Considerations
This intervention is intended for the care of individuals with a condition of particularly high severity in terms of impact on length of life and/or quality of life.
This intervention is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness.
This intervention is the first to offer any improvement for patients with this condition.
Compared to best supportive care, there is significant uncertainty about the long-term risk of serious side effects of this intervention.
Compared to best supportive care, there is significant uncertainty about the magnitude or durability of the long-term benefits of this intervention.
There are additional contextual considerations that should have an important role in judgments of the value of this intervention.

5.1 Potential Other Benefits

MS-related disability reduces patients' capacity to independently pursue many of their daily activities. In the MS Coalition's survey (described in Section 1.4), patients reported that they required assistance for personal care (e.g., bathing and dressing: 24%), cleaning their homes (59%), cooking (43%), and transportation (48%); less than a third of respondents replied that they did *not* require assistance carrying out these activities. MS symptoms and treatment also caused nearly three quarters (72%) of employed respondents to miss at least one day of work in the last year and 51% of respondents reported that their disability prevented them from being able to work at all.

As described in Section 3, siponimod reduced the risk of EDSS progression and decreased relapse activity in the EXPAND trial. Although the EXPAND trial did not evaluate whether siponimod positively affects patients' independence and productivity, delayed disability progression and reduced MS exacerbations hold promise to also improve patients' ability to sustain their careers and their daily routines for a longer duration of time.

In addition to losses in patient productivity, the MS Coalition's survey revealed that primary caregivers also took time off of work to attend to the symptoms or treatment of the patient they

were caring for; just 25% of patients reported that their primary caregiver did *not* need to miss work on account of caregiving responsibilities in the past year. Thus, a therapy that delays or prevents disability progression in patients with SPMS is likely to also offer a downstream benefit to their caregivers.

Other therapies commonly used in SPMS require infusions or injections. Siponimod is an oral therapy.

5.2 Contextual Considerations

The secondary progressive course of MS is characterized by an insidious worsening of neurologic disability that accrues irrespective of relapse activity. There is a paucity of effective treatments available to treat SPMS, especially for the non-active phenotypic classification. SPMS is a condition with a high lifetime burden of illness and severe impact on quality of life. In this context, any therapy that offers some improvement is of great interest to patients as well as their caregivers and physicians.

In the MS Coalition's survey, approximately 95% of participants responded that they would be interested—approximately 50% specified they would be *extremely* interested—in a new therapy that could stabilize or improve SPMS symptoms, prevent relapse, and help them maintain their current levels of activity. However, 71% reported that uncertainty about the long-term risks of a new drug for SPMS might prevent them from being adherent. Notwithstanding the EXPAND trial's promising results, further study of siponimod is warranted to resolve remaining uncertainties about its long-term benefits and safety.

There is an unmet need for treatments of non-active SPMS. Despite the FDA approved indications for siponimod, it remains possible that siponimod has some efficacy on progression in patients with non-active SPMS.

6. Value-Based Price Benchmarks

This report evaluated siponimod as treatment for SPMS. As the FDA-approved indication for siponimod is for relapsing forms of MS, and active SPMS is only a portion of the patients with SPMS and does not include RRMS, we are not providing value-based price benchmarks for siponimod as part of this review. ICER is likely to evaluate siponimod in the future when we re-review therapies for relapsing forms of MS.

7. Potential Budget Impact

As discussed above with regard to value-based price benchmarks, the FDA-approved indication for siponimod (relapsing forms of MS) is different from the focus of this review (SPMS). As such, we are not providing calculations related to the potential budget impact of siponimod.

8. Summary of the Votes and Considerations for Policy

8.1 About the Midwest CEPAC Process

During Midwest CEPAC public meetings, the Midwest CEPAC Panel deliberates and votes on key questions related to the systematic review of the clinical evidence, an economic analysis of the applications of treatments under examination, and the supplementary information presented. Panel members are not pre-selected based on the topic being addressed and are intentionally selected to represent a range of expertise and diverse perspectives.

Acknowledging that any judgment of evidence is strengthened by real-life clinical and patient perspectives, subject matter experts are recruited for each meeting topic and provide input to Midwest CEPAC Panel members before the meeting to help clarify their understanding of the different interventions being analyzed in the evidence review. The same clinical experts serve as a resource to the Midwest CEPAC Panel during their deliberation and help to shape recommendations on ways the evidence can apply to policy and practice.

After the Midwest CEPAC Panel votes, a policy roundtable discussion is held with the Midwest CEPAC Panel, clinical experts, patient advocates, payers, and when feasible, manufacturers. The goal of this discussion is to bring stakeholders together to apply the evidence to guide patient education, clinical practice, and coverage and public policies. Participants on policy roundtables are selected for their expertise on the specific meeting topic, are different for each meeting, and do not vote on any questions.

At the May 23, 2019 meeting, the Midwest CEPAC Panel discussed issues regarding the application of the available evidence to help patients, clinicians, and payers address important questions related to the use of siponimod for secondary progressive multiple sclerosis (SPMS). Following the evidence presentation and public comments (public comments from the meeting can be accessed at https://www.youtube.com/watch?v=oydoIunMhEk&t=1s starting at minute 1:16:42), the Midwest CEPAC Panel voted on key questions concerning the comparative clinical effectiveness, comparative value, and potential other benefits and contextual considerations related to esketamine. These questions are developed by the ICER research team for each assessment to ensure that the questions are framed to address the issues that are most important in applying the evidence to support clinical practice, medical policy decisions, and patient decision-making. The voting results are presented below, along with specific considerations mentioned by Midwest CEPAC Panel members during the voting process.

In its deliberations and votes related to value, the Midwest CEPAC Panel considered the individual patient benefits, and incremental costs to achieve such benefits, from a given intervention over the long term.

There are four elements to consider when deliberating on long-term value for money (see Figure 8.1 below):

1. Comparative clinical effectiveness is a judgment of the overall difference in clinical outcomes between two interventions (or between an intervention and placebo), tempered by the level of certainty possible given the strengths and weaknesses of the body of evidence. The Midwest CEPAC uses the ICER Evidence Rating Matrix as its conceptual framework for considering comparative clinical effectiveness.

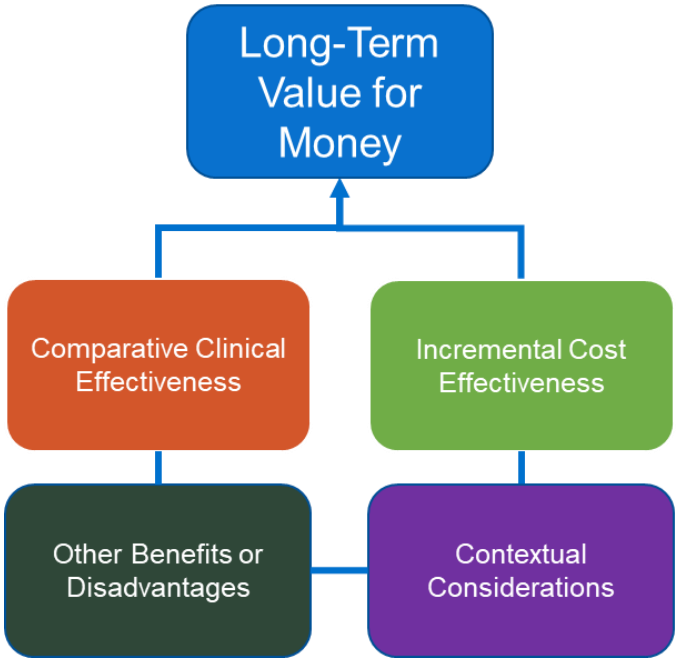
2. Estimated incremental cost-effectiveness is the average incremental cost per patient of one intervention compared to another to achieve a desired "health gain," such as an additional stroke prevented, case of cancer diagnosed, or gain of a year of life. Alternative interventions are compared in terms of cost per unit of effectiveness, and the resulting comparison is presented as a cost-effectiveness ratio. Relative certainty in the cost and outcome estimates continues to be a consideration. As a measure of cost-effectiveness, the Midwest CEPAC voting panel follows common academic and health technology assessment standards by using cost per quality-adjusted life year (QALY), with formal voting on "long-term value for money" when the base case incremental cost-effectiveness ratio is between $50,000 per QALY and $175,000 per QALY.

3. Potential other benefits refer to any significant benefits or disadvantages offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that would not have been considered as part of the evidence on comparative clinical effectiveness. Examples of potential other benefits include better access to treatment centers, mechanisms of treatment delivery that require fewer visits to the clinician's office, treatments that reduce disparities across various patient groups, and new potential mechanisms of action for treating clinical conditions that have demonstrated low rates of response to currently available therapies. Other disadvantages could include increased burden of treatment on patients or their caregivers. For each intervention evaluated, it will be open to discussion whether potential other benefits or disadvantages such as these are important enough to factor into the overall judgment of long-term value for money. There is no quantitative measure for potential other benefits or disadvantages.

4. Contextual considerations include ethical, legal, or other issues (but not cost) that influence the relative priority of illnesses and interventions. Examples of contextual considerations include whether there are currently any existing treatments for the condition, whether the

condition severely affects quality of life or not, and whether there is significant uncertainty about the magnitude of benefit or risk of an intervention over the long term. There is no quantitative measure for contextual considerations.

Figure 8.1. Conceptual Structure of Long-term Value for Money



8.2 Voting Results

information on the deliberation surrounding the votes can be found in the full report.

1. In patients with ***active*** SPMS, is the evidence adequate to demonstrate that the net health benefit provided by siponimod is superior to that provided by best supportive care?

Yes: 15 votes	No: 2 votes

A majority of the CEPAC Council voted that the evidence is adequate to demonstrate that the net health benefit provided by siponimod is superior to that provided by best supportive care in patients with active SPMS. Several Council members who voted in the affirmative noted that they considered the evidence to be adequate but not overwhelming, citing "bias" in the EXPAND trial, a small sample size, and absence of pre-specific subgroups. One Council member who voted in the negative cited methodologic concerns regarding enrollment and analysis in the clinical trial and lack of knowledge about long-term benefits and harms as informing his vote.

2. In patients with ***non-active*** SPMS, is the evidence adequate to demonstrate that the net health benefit provided by siponimod is superior to that provided by best supportive care?

Yes: 0 votes	***No: 17 votes***

The Council unanimously judged that the evidence is not adequate to demonstrate that the net health benefit provided by siponimod is superior to that provided by best supportive care in patients with non-active SPMS. Several Council members were concerned that the clinical benefit was based solely on a subgroup analysis of the EXPAND trial and noted that the finding was not statistically significant in the non-active SPMS population. Others cited the FDA's concerns surrounding trial methodology, unclear benefits, and side effects as influencing their vote.

3. For patients with SPMS, does siponimod offer one or more of the following potential "other benefits or disadvantages" versus best supportive care not adequately captured in the clinical trial data or base-case cost-effectiveness model results?" (select all that apply)

This intervention will significantly reduce caregiver or broader family burden.	6/17
This intervention offers a novel mechanism of action or approach that will allow successful treatment of many patients for whom other available treatments have failed.	0/17
This intervention will have a significant impact on improving patients' ability to return to work and/or their overall productivity.	1/17
There are other important benefits or disadvantages that should have an important role in judgments of the value of this intervention.	4/17

No Council members voted that siponimod offers a novel mechanism of action, citing that fingolimod works through the same mechanism. Council members discussed whether siponimod provides any advantages in terms of dosing or route of administration, and a clinical expert present at the meeting noted that siponimod is more complex than fingolimod in terms of dosing.

Four Council members voted that there are other important benefits or disadvantages that should have an important role in judgments of the value of siponimod. One Council member noted that there are clinical benefits, such as improvements in social isolation and fatigue, that are not captured by standard outcome measures in trials. Multiple Council members noted their concern around long-term harms of siponimod, and one noted that he considered this an "other disadvantage."

4. For patients with SPMS, are any of the following contextual considerations important in assessing siponimod's long-term value for money versus best supportive care? (select all that apply)

This intervention is intended for the care of individuals with a condition of particularly high severity in terms of impact on length of life and/or quality of life.	12/17
This intervention is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness.	13/17
This intervention is the first to offer any improvement for patients with this condition.	2/17
There is significant uncertainty about the long-term risk of serious side effects of this intervention.	10/17
There is significant uncertainty about the magnitude or durability of the long-term benefits of this intervention.	13/17
There are additional contextual considerations that should have an important role in judgments of the value of this intervention.	5/17

Thirteen Council members voted that siponimod is intended for the care of patients with a condition that represents a high lifetime burden of illness. Multiple Council members who did not vote for this category noted that they do believe that SPMS represents a particularly high lifetime burden of illness but interpreted the question in different ways. The moderator's presentation of this vote was done somewhat differently from in past ICER meetings and this led to some members voting "no" if they felt that the burdens were captured in the economic model. This was not the intent, and ICER will review how best to describe this vote to the panels. For this report, readers should recognize that panel members overwhelmingly expressed that SPMS has a particularly high lifetime burden of illness.

Ten Council members voted that there is significant uncertainty about the long-term risk of serious side effects and thirteen Council members voted that there is significant uncertainty about the long-term benefits of siponimod, noting the paucity of long-term data.

Five Council members voted that there are additional contextual considerations that should be taken into account when evaluating this intervention. One of these members stated that it is important to consider that there are other treatments available for reducing relapses in patients with active forms of MS. Another noted that SPMS does represent a high lifetime burden of illness, but it is unclear whether siponimod provides long-term benefit to reduce this burden.

Long-term Value for Money

As described in ICER's value assessment framework, questions on long-term value for money are subject to a value vote when incremental cost-effectiveness ratios for the interventions of interest are between $50,000 and $175,000 per QALY in the primary "base case" analysis. The base case estimates of the cost per QALY for siponimod exceed the higher end of this range, and therefore the treatment is deemed "low long-term value for money" without a vote unless the CEPAC determines in its discussion that the Evidence Report base case analysis does not adequately reflect the most probable incremental cost-effectiveness ratio for siponimod.

8.3 Roundtable Discussion and Key Policy Implications

Following its deliberation on the evidence, the Midwest CEPAC Panel engaged in a moderated discussion with a policy roundtable about how best to apply the evidence on siponimod for SPMS to policy and practice. The policy roundtable members included two patient advocates, two clinical experts, one payer, and the manufacturer of siponimod. The discussion reflected multiple perspectives and opinions, and therefore, none of the statements below should be taken as a consensus view held by all participants. The names of the Policy Roundtable participants are shown below, and conflict of interest disclosures for all meeting participants can be found in Appendix H.

Table 8.1. Policy Roundtable Members

Name	Title and Affiliation
Bruce A. Cohen, MD	Professor, Davee Department of Neurology and Clinical Neurological Sciences, Northwestern University Feinberg School of Medicine
Jeremy Fredell, PharmD, BCPS	Director Trend Solutions – Drug Trend & Formulary, Express Scripts
Annette Langer- Gould, MD, PhD	Regional Lead for Clinical and Translational Neuroscience, Kaiser Permanente/Southern California Permanente Medical Group
Ann Moore	Patient Advocate
Hollie Schmidt, MS	Vice President of Scientific Operations, Accelerated Cure Project for Multiple Sclerosis
Gustavo Suarez Zambrano, MD	Novartis

The roundtable discussion was facilitated by Dr. Steven Pearson, MD, MSc, President of ICER. The main themes and recommendations from the discussion are organized by audience and summarized below.

Manufacturers

1. To provide fair value to patients and the health system, the manufacturer should lower the price of siponimod so it aligns with the added value it brings to patients.

The high price of siponimod imposes an undue burden on patients that is disproportionate to the value it provides. The choice of siponimod's list price is not consistent with efforts from the patient community and other stakeholders to seek prices that align more fairly with the added benefits to patients and will lead to continued unnecessary financial burden on patients and the health system.

Payers

2. Evidence and clinical testimony suggested that siponimod does not have a unique role in therapy for any phenotype of MS, including active SPMS. Given its similarities to fingolimod, siponimod should be considered amongst a group of highly effective disease modifying therapies (DMTs) for relapsing forms of MS, including fingolimod, alemtuzumab, natalizumab, and ocrelizumab.[14,32]

Although a therapy that provides a benefit to patients with non-active SPMS could play a unique role in the MS treatment landscape, evidence to support siponimod's effectiveness for the treatment of non-active SPMS is currently insufficient. Moreover, no evidence or clinical testimony suggested that siponimod should be viewed in a formulary design as having a unique role for *active* SPMS compared to other DMTs.

3. Payers should offer preferential formulary status to highly effective DMTs with superior safety profiles for patients early in their disease course (i.e., RRMS). For many patients, the evidence is not adequate to determine which DMT would be superior as a first option; therefore, it is reasonable for payers to consider step therapy as a mechanism to achieve lower costs without harming patients. However, any step therapy program must be administered in a way that does not require patients to re-try drugs they have had an inadequate response to in the past, nor prevent clinicians and patients from seeking rapid exceptions based on transparent, evidence-based criteria.

Evidence suggests early treatment with highly effective DMTs can delay conversion to SPMS.[14] It is reasonable for payers to implement step therapy protocols during the RRMS phase of MS that prioritize the use of highly effective DMTs, while weighing both safety and cost considerations. Such protocols should follow a continuum that is maintained through the *active* SPMS disease course, as it would not be reasonable to initiate a new step therapy protocol once a patient receives an SPMS diagnosis. Patients with active SPMS should not be required to step through less effective platform drugs, such as beta interferons or glatiramer acetate.[14]

4. Payers may wish to specifically consider granting preferential formulary status to fingolimod when its generic formulation comes to the market.

We heard no clinical testimony that siponimod has special safety or effectiveness benefits that would prevent step therapy through fingolimod from being a reasonable coverage plan for highly active disease.

Patient Advocacy Organizations

5. Patient organizations should view their longer-term mission in support of patients to include active engagement with manufacturers to demand reasonable value-based pricing of the therapies that patients and their families helped bring to the market.

Patient advocacy groups for MS are well organized and played a leading role in funding, organizing, and promoting the research that led to effective treatments. Patient groups should feel proud of this accomplishment. They should also accept a broader mission on behalf of patients by exercising their power to influence pricing in order to improve long-term access and affordability. It is evident across the health system that when prices are viewed as fair and reasonable, access is improved in the short term without vitiating the incentives that will draw further investment and research.

Specialty Societies

6. Testimony from patients and clinicians suggested that patients may benefit more from treatment that is provided by clinicians who are experts in the diagnosis and management of different forms of MS.

Recognizing the inherent difficulties surrounding MS phenotyping, particularly in settings where few MS patients are treated, the management of patients with MS should be led by MS specialists when such specialists are available. MS specialists are better equipped to disentangle RRMS from SPMS, to advise patients on the potential benefits and risks of therapy, and to make the difficult determination of when discontinuation of a DMT may be warranted. Moreover, the need for expertise is notable with siponimod, the drug of focus for this review. Siponimod requires multiple assessments (genotypic, cardiac, ophthalmologic) prior to initiation, may require additional monitoring in patients with certain comorbidities, and because of its similarity to fingolimod there are potential safety concerns around discontinuation and re-initiation of therapy.

7. Individual clinicians and clinical specialty societies should assume a broad leadership role in advocating for patients by taking four actions: 1) highlight and work to address insurance barriers to appropriate care; 2) be vocal witnesses to the negative effects of excessive prices on patients and families, particularly the underserved; 3) integrate considerations of value into clinical guidelines; and 4) embody a broad model of professionalism that calls upon clinicians to work towards a health system that improves access and provides a sustainable model for future innovation through fair pricing.

Regulators

8. The FDA should encourage the standardization and implementation of outcome measures that are interpretable, sensitive, and relevant to an SPMS patient population.

Although the EDSS is a widely used instrument for measuring disability progression, its limitations include nonlinearity, insensitivity to small changes, susceptibility to intra- and interrater variability, a disproportionate emphasis on walking, and underestimation of other functional systems such as cognitive impairment. Other metrics may better capture the outcomes that are important to patients, including symptom relief, upper extremity function, quality of life, cognition and other patient-reported outcomes, and may be more sensitive to changes that occur during the SPMS disease course.

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This is the first ICER review of siponimod.

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APPENDICES

Appendix A. Search Strategies and Results

Table A1. PRISMA 2009 Checklist

	#	Checklist Item
TITLE		
Title	1	Identify the report as a systematic review, meta-analysis, or both.
ABSTRACT		
Structured Summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.
INTRODUCTION		
Rationale	3	Describe the rationale for the review in the context of what is already known.
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).
METHODS		
Protocol and Registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.
Eligibility Criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.
Information Sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.
Study Selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).
Data Collection Process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.
Data Items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.
Risk of Bias in Individual Studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.

Summary Measures	13	State the principal summary measures (e.g., risk ratio, difference in means).
Synthesis of Results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.
Risk of Bias Across Studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).
Additional Analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.
RESULTS		
Study Selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.
Study Characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.
Risk of Bias Within Studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).
Results of Individual Studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.
Synthesis of Results	21	Present the main results of the review. If meta-analyses are done, include for each, confidence intervals and measures of consistency.
Risk of Bias Across Studies	22	Present results of any assessment of risk of bias across studies (see Item 15).
Additional Analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).
DISCUSSION		
Summary of Evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.
FUNDING		
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.

From: Moher D, Liberati A, Tetzlaff J, Altman DG. The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

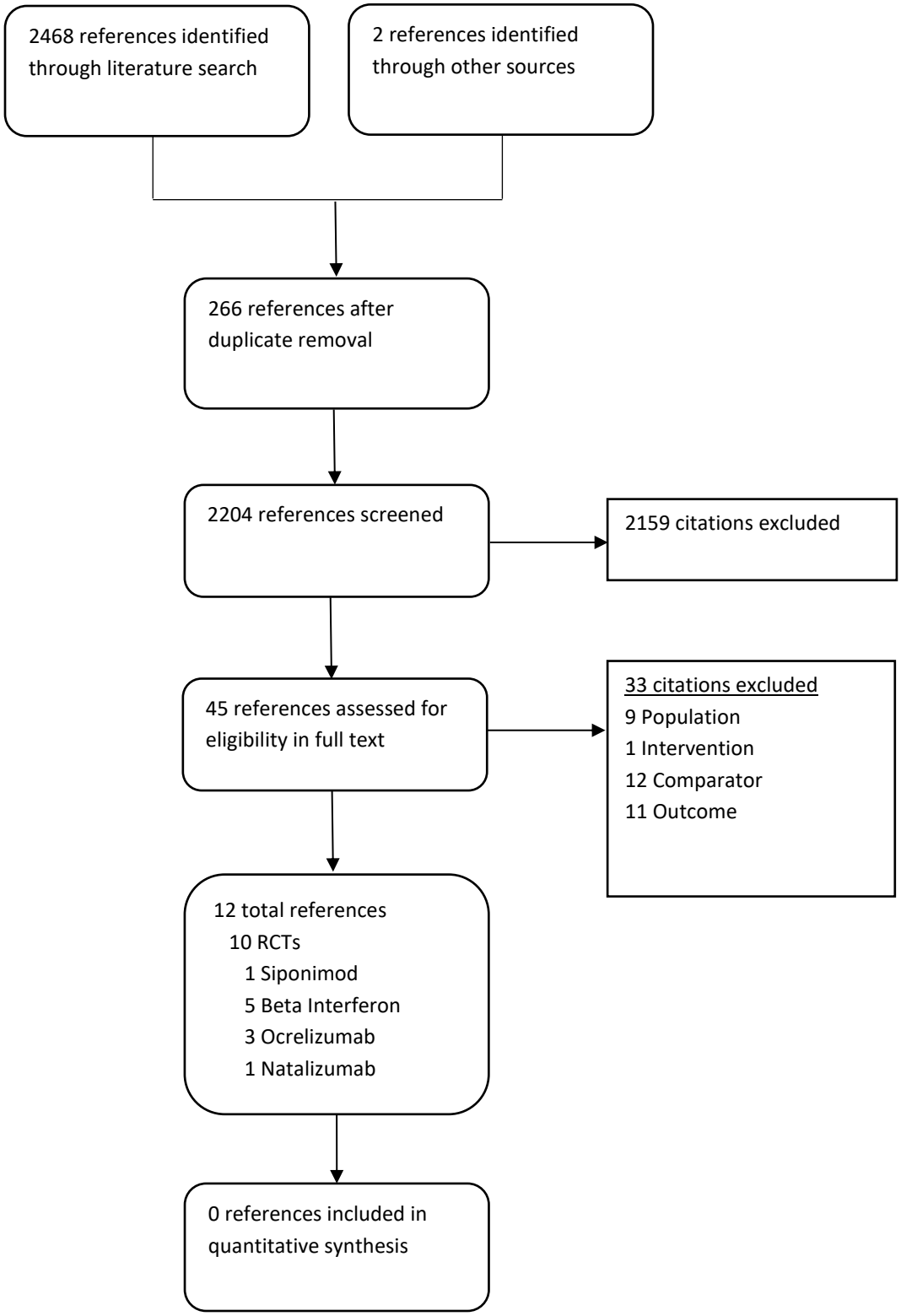
Table A2. Search Strategy of Ovid Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R) 1946 to Present

1	exp multiple sclerosis/dt
2	'multiple sclerosis'.ti,ab.
3	1 or 2
4	(siponimod or baf312 or 'baf-312' or 'baf 312').ti,ab.
5	natalizumab/tu or (natalizumab or antegren or tysabri).ti,ab.
6	(ocrelizumab or ocrevus).ti,ab.
7	exp interferon-beta/tu
8	('interferon beta' or 'interferon beta1' or 'beta-1 interferon' or 'beta 1 interferon' or 'interferon beta-1b' or 'interferon beta-1a' or ('ifn-' adj4 1a) or ('ifn-' adj4 1b) or (interferon adj4 beta) or (interferon adj4 1a) or (interferon adj4 1b) or (avonex or extavia or rebif or plegridy or betaferon or betaseron or peginterferon)).ti,ab.
9	4 or 5 or 6 or 7 or 8
10	3 and 9
11	limit 10 to (addresses or autobiography or bibliography or biography or case reports or classical article or clinical conference or clinical trial, phase i or comment or congresses or consensus development conference or consensus development conference, nih or dataset or dictionary or directory or duplicate publication or editorial or equivalence trial or "expression of concern" or festschrift or government publications or guideline or historical article or interactive tutorial or interview or introductory journal article or lectures or legal cases or legislation or letter or news or newspaper article or overall or patient education handout or periodical index or personal narratives or portraits or practice guideline or published erratum or "research support, american recovery and reinvestment act" or research support, nih, extramural or research support, nih, intramural or research support, non us gov't or research support, us gov't, non phs or research support, us gov't, phs or retracted publication or "retraction of publication" or "review" or "scientific integrity review" or technical report or twin study or validation studies or video-audio media or webcasts)
12	10 not 11
13	limit 12 to (animals or (humans and animals))
14	12 not 13
15	limit 14 to english language

Table A3. Search Strategy of EMBASE

#1	‘multiple sclerosis’/de
#2	'multiple sclerosis':ti,ab
#3	#1 OR #2
#4	'siponimod'/de
#5	('siponimod' OR 'baf312' OR 'baf 312' OR 'baf-312'):ti,ab
#6	'beta1a interferon'/de OR ‘recombinant beta interferon’/de OR ‘interferon beta serine‘/de OR ‘peginterferon beta1a’/de OR 'natalizumab'/de OR 'ocrelizumab'/de
#7	'interferon beta 1*':ti,ab OR 'interferon beta-1*':ti,ab OR 'interferon beta 1*':ti,ab OR 'interferon beta1*':ti,ab OR ('ifn-' NEAR/4 1a):ti,ab OR ('ifn-' NEAR/4 1b):ti,ab OR (interferon NEAR/4 beta):ti,ab OR (interferon NEAR/4 1a):ti,ab OR (interferon NEAR/4 1b):ti,ab
#8	'avonex':ti,ab OR 'avonex pen':ti,ab OR ‘extavia’:ti,ab OR 'rebif':ti,ab OR 'plegridy':ti,ab OR ‘betaferon’:ti,ab OR ‘betaseron’:ti,ab
#9	'natalizumab':ti,ab OR 'tysabri':ti,ab OR 'antegren':ti,ab
#10	'ocrelizumab':ti,ab OR 'ocrevus':ti,ab
#11	#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10
#12	#3 AND #11
#13	#12 AND ('case report'/de OR 'human cell'/de OR 'human tissue'/de OR 'in vitro study'/de)
#14	#12 NOT #13
#15	#14 AND ('chapter'/it OR 'conference abstract'/it OR 'conference paper'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'review'/it OR 'short survey'/it)
#16	#14 NOT #15
#17	#16 AND [english]/lim
#18	#17 AND [medline]/lim
#19	#17 NOT #18
#20	#19 AND ('animal'/de OR 'nonhuman'/de OR 'animal experiment'/de)
#21	#19 NOT #20

Figure A1. PRISMA Flow Chart Showing Results of Literature Search for Secondary Progressive Multiple Sclerosis



Appendix B. Previous Systematic Reviews and Technology Assessments

We did not identify any completed health technology assessments or peer-reviewed systematic reviews of siponimod in secondary progressive multiple sclerosis. However, there is one ongoing technology assessment in this population that is cited below.

NICE: Siponimod For Treating Secondary Progressive Multiple Sclerosis [ID1304], Expected publication date to be confirmed

https://www.nice.org.uk/guidance/gid-ta10436/documents/draft-scope-pre-referral

NICE is currently appraising the clinical and cost effectiveness of siponimod for treating secondary progressive multiple sclerosis.

Appendix C. Ongoing Studies

Title/ Trial Sponsor	Study Design	Comparators	Patient Population	Primary Outcomes	Estimated Completion Date
Siponimod					
Safety and Tolerability of Conversion from Oral or Injectable Disease Modifying Therapies to Dose-Titrated Oral Siponimod in Advancing RMS Patients (EXCHANGE) Novartis Pharmaceuticals NCT03623243	Phase 3b Open-label, multi-center, single arm study Estimated Enrollment: 300	Siponimod Dose: 2mg	Inclusion Criteria: – Signed informed consent – Male or female aged 18 to 65 years – Patients with advancing RMS – Prior history of relapsing MS, with or without progressive features – EDSS score of > 2.0 – 6.5 – Continuously treated with oral or injectable RMS DMTs Exclusion Criteria: – Pregnant or nursing – Patients with medically unstable condition – History of hypersensitivity	Primary Outcomes: Safety and tolerability after converting from DMTs Secondary Outcomes: – Number of patients satisfied with treatment – Adherence	January 2020

Source: www.ClinicalTrials.gov (NOTE: studies listed on site include both clinical trials and observational studies)

Appendix D. Comparative Clinical Effectiveness Supplemental Information

We performed screening at both the abstract and full-text level. A single investigator screened all abstracts identified through electronic searches according to the inclusion and exclusion criteria described earlier. We did not exclude any study at abstract-level screening due to insufficient information. For example, an abstract that did not report an outcome of interest would be accepted for further review in full text. We retrieved the citations that were accepted during abstract-level screening for full text appraisal. One investigator reviewed full papers and provided justification for exclusion of each excluded study.

We used criteria published by the US Preventive Services Task Force (USPSTF) to assess the quality of RCTs and comparative cohort studies, using the categories "good," "fair," or "poor" (see Appendix Table F2).[78] Guidance for quality ratings using these criteria is presented below, as is a description of any modifications we made to these ratings specific to the purposes of this review.

Good: *Meets all criteria: Comparable groups are assembled initially and maintained throughout the study; reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; all important outcomes are considered; and appropriate attention is paid to confounders in analysis. In addition, intention to treat analysis is used for RCTs.*

Fair: *Studies were graded "fair" if any or all of the following problems occur, without the fatal flaws noted in the "poor" category below: Generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred with follow-up; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are addressed. Intention to treat analysis is done for RCTs.*

Poor: *Studies were graded "poor" if any of the following fatal flaws exists: Groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied equally among groups (including not masking outcome assessment); and key confounders are given little or no attention. For RCTs, intention to treat analysis is lacking.*

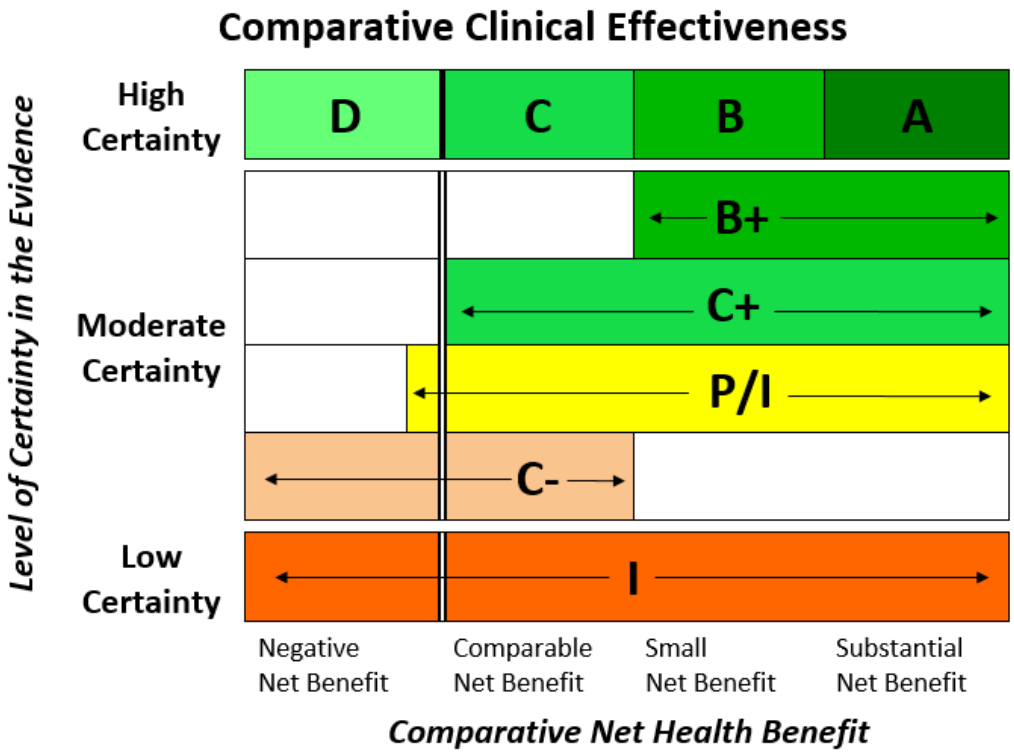
Note that case series are not considered under this rating system – because of the lack of comparator, these are generally considered to be of poor quality.

ICER Evidence Rating

We used the ICER Evidence Rating Matrix (see Figure D1) to evaluate the evidence for a variety of outcomes. The evidence rating reflects a joint judgment of two critical components:

a) The **magnitude** of the difference between a therapeutic agent and its comparator in "net health benefit" – the balance between clinical benefits and risks and/or adverse effects AND
b) The level of **certainty** in the best point estimate of net health benefit.[79]

Figure D1. ICER Evidence Rating Matrix



A = "Superior" *- High certainty of a substantial (moderate-large) net health benefit*
B = "Incremental" *- High certainty of a small net health benefit*
C = "Comparable" *- High certainty of a comparable net health benefit*
D = "Negative" *- High certainty of an inferior net health benefit*
B+ = "Incremental or Better" *- Moderate certainty of a small or substantial net health benefit, with high certainty of at least a small net health benefit*
C+ = "Comparable or Better" *- Moderate certainty of a comparable, small, or substantial net health benefit, with high certainty of at least a comparable net health benefit*
P/I = "Promising but Inconclusive" *- Moderate certainty of a comparable, small, or substantial net health benefit, and a small (but nonzero) likelihood of a negative net health benefit*
C- = "Comparable or Inferior" *- Moderate certainty that the point estimate for comparative net health benefit is either comparable or inferior*
I = "Insufficient" *- Any situation in which the level of certainty in the evidence is low*

Evidence Tables

Table D1. Study Design

Reference & Study Name	Study Design	Intervention & Dose	N	Follow-up	Inclusion Criteria					
					Age Range (Years)	SPMS Definition & Duration	EDSS	Disability Progression	Relapse History	Other Inclusion/Exclusion Criteria
Siponimod										
Kappos 2018[19] EXPAND	Phase 3 Randomized, international, double-blind, placebo-controlled trial with open-label extension	1) Siponimod: 2mg (oral) once daily with dose titration on days 1-6 2) Placebo	1651	Median time on study: 21 months	18 – 60	Progressive increase in disability of ≥6 months duration in absence of, or independent of relapses	3.0 – 6.5	Documented EDSS progression in the 2 years prior to study of ≥1 point for patients with EDSS <6.0, and ≥0.5 point for patients with EDSS ≥6.0 at screening	No evidence of relapse in 3 months prior to randomization	Inclusions: – History of RRMS (2010 McDonald criteria) Exclusions: – CYP2C9*3/*3 genotype
Natalizumab										
Kapoor 2018[30] ASCEND	Phase 3 Part 1: Randomized, international, double-blind, placebo-controlled trial Part 2: Two-year, open label extension (optional)	1) Natalizumab: 300 mg (IV) every 4 weeks 2) Placebo	889	*Median total follow-up (including parts 1 & 2), weeks (range)* 1) Natalizumab: 160 (118-213) 2) Placebo: 157 (108-221)	18 – 58	RRMS followed by progression of disability independent of or not explained by relapses for ≥2 years	3.0 – 6.5	Disability progression not related to clinical relapses during the year before enrollment	No clinical relapses up to 3 months before randomization	Inclusions: – Natalizumab naïve patients – MS Severity Score of ≥4 Exclusions: – RRMS or PPMS diagnosis – T25WT >30 seconds during screening period

Reference & Study Name	Study Design	Intervention & Dose	N	Follow-up	Inclusion Criteria					
					Age Range (Years)	SPMS Definition & Duration	EDSS	Disability Progression	Relapse History	Other Inclusion/Exclusion Criteria
Beta Interferons										
Kappos 1998[21] EU Trial	Randomized, European, double-blind, placebo-controlled trial	1) Interferon beta-1b: 0.5 mL [4 million IU] (SC) for first 2 weeks; 1.0 mL [8 million IU] every other day thereafter 2) Placebo	718	*Mean follow-up at interim/ termination cut-off (days)* 1) Interferon beta-1b: 901/1068 2) Placebo: 892/1054 *Planned study duration*: 3 years	18 – 55	A period of deterioration, independent of relapses, sustained for ≥6months, that followed a period of RRMS	3.0 – 6.5	≥1.0 increase in EDSS in the previous 2 years (or ≥2 relapses in the previous 2 years)	A recorded history of ≥2 relapses in the previous 2 years (or ≥1.0 increase in EDSS in the previous 2 years)	Inclusions: – Superimposed relapses allowed Exclusions: – Immunosuppressive or immunomodulatory treatment and other putative treatments for MS for defined periods before entry

Reference & Study Name	Study Design	Intervention & Dose	N	Follow-up	Inclusion Criteria					
					Age Range (Years)	SPMS Definition & Duration	EDSS	Disability Progression	Relapse History	Other Inclusion/Exclusion Criteria
Panitch 2004[22] N. American	Randomized, North-American, double-blind, placebo-controlled trial	1) Interferon beta-1b: 250 µg (SC) every other day; initiated 62.5 µg (0.25 mL) and increased dosing 0.25 mL each week until max. dose achieved 2) Interferon beta-1b: 160 µg (SC) every other day; initiated 0.15-0.25 mL and escalated by 0.10-0.25 mL each week until max. dose achieved 3) Placebo	939	*Mean duration of follow-up* 1) Interferon beta-1b (250 µg): 998 days 2) Interferon beta-1b (160 µg): 1,013 days c) 3) Placebo: 1,003 days	18 - 65	*See Disability Progression and Relapse History*	3.0 – 6.5	– Increase in EDSS score ≥1.0 point in the 2 years prior to screening (≥0.5 points for subjects with EDSS score of 6.5) – Progressive deterioration sustained for at least 6-months	A history of ≥1 relapse followed by progressive deterioration sustained for at least 6-months	Inclusions: – Clinically definite or laboratory supported definite MS ≥2 years duration Exclusions: – Received treatment with corticosteroids – Previously treated with interferon beta – Received cytotoxic or immunosuppressive therapy
Li 2001[125] SPECTRIMS	Randomized, international, double-blind, placebo-controlled trial	1) Interferon beta-1a: 44 µg (SC) 3 times a week 2) Interferon beta-1a: 22 µg (SC) 3 times a week 3) Placebo	618	92.4% of patients had full follow-up data over 3 years	18 – 55	*See Disability Progression and Relapse History*	3.0 – 6.5	Progressive deterioration of disability for ≥6 months with an ≥1 EDSS point increase in last 2 years (or 0.5 point for scores of 6.0 and 6.5)	With or without superimposed exacerbation following initial RR course	Inclusions: – Pyramidal functional score ≥2 Exclusions: – Immunosuppressive or immunomodulatory treatments during prior 3-12 months – Prior treatment with interferon, or total lymphoid irradiation – Corticosteroid use or disease exacerbation in previous 8 weeks

Reference & Study Name	Study Design	Intervention & Dose	N	Follow-up	Inclusion Criteria					
					Age Range (Years)	SPMS Definition & Duration	EDSS	Disability Progression	Relapse History	Other Inclusion/Exclusion Criteria
Andersen 2004[25] Nordic Trial	Phase 3 Randomized, double-blind, placebo-controlled trial in Denmark, Norway, Finland, and Sweden	1) Interferon beta-1a: 22 µg (SC) once weekly 2) Placebo	371	301 patients (83%) completed the 3-year double-blind phase of the study	18 – 65	Prior RRMS and progressive deterioration with or without superimposed relapses	<7.0	Progressive deterioration of disability ≥6 months with EDSS increase of ≥1.0 point in previous 4 years (or 0.5 points if the entry EDSS was 6.0 or 6.5)	With or without superimposed exacerbations	Inclusions: – Clinically definite MS ≥1 year – History of RRMS – Stable neurological condition for 4 weeks preceding study day 1 Exclusions: – Similar to those of previous interferon beta trials
Cohen 2002[26] IMPACT	Randomized, international, double-blind, placebo-controlled trial	1) Interferon beta-1a: 60 µg (SC) once weekly 2) Placebo	436	24 months	18 – 60	*See Disability Progression and Relapse History*	3.5 – 6.5	Clinically definite SPMS	With or without relapses	Inclusions: – Disease progression over past year – Lesions (confirmed with MRI) Exlusions: – PPMS – Inability to perform component tests of MSFC
Ocrelizumab										
Montalban, 2017[33] ORATORIO	Phase 3 Randomized, placebo-controlled trial	1) Ocrelizumab: 600 mg (IV) every 24 weeks 2) Placebo	732	1) Ocrelizumab: 217 weeks 2) Placebo: 216 weeks	18 - 55	NR	3.0 – 6.5	NR	*See exclusion criteria*	Inclusions: – Duration of MS symptoms less than 15 years (if EDSS ≤5) – Documented history or the presence at screening of an elevated IgG index Exclusions: – History of RRMS – SPMS or progressive-relapsing MS

Reference & Study Name	Study Design	Intervention & Dose	N	Follow-up	Inclusion Criteria					
					Age Range (Years)	SPMS Definition & Duration	EDSS	Disability Progression	Relapse History	Other Inclusion/Exclusion Criteria
Hauser 2017[32] OPERA I + II (High risk of SPMS subgroup analysis)[32], 1002; [34]	Phase 3 Randomized, international, double-blind, placebo-controlled trial	1) Ocrelizumab: 600mg (IV) every 24 weeks 2) Interferon beta-1a: 44 µg (SC) three times weekly 3) Matching SC or IV placebo, as appropriate	355 (Total N: 1656)	96 weeks	18-55	Population at potentially higher risk of SPMS based on baseline EDSS ≥4.0 and pyramidal Kurtzke Functional System Score ≥25	0 – 5.5 at screening	NR	At least two documented clinical relapses within the previous 2 years, or one clinical relapse within the year before screening	Inclusions: – No neurologic worsening for at least 30 days before both screening and baseline Exclusions: – PPMS diagnosis – Previous treatment with any B-cell–targeted therapy or other immunosuppressive medication

EDSS: Expanded Disability Status Scale, IV: intravenously, max: maximum, MS: multiple sclerosis, MSFC: Multiple Sclerosis Functional Composite, PPMS: primary-progressive multiple sclerosis, RR: relapsing-remitting, RRMS: relapsing-remitting multiple sclerosis, SC: subcutaneously, SPMS: secondary-progressive multiple sclerosis

Table D2. Study Quality Metrics for EXPAND Trial of Siponimod

Reference & Study Name	Adequate Randomization	Allocation Concealment	Patient Blinding	Staff Blinding	Outcome Adjudication Blinding	Completeness of Follow-up	Intention to Treat Analysis	Incomplete Data Addressed	Selective Outcome Reporting	Industry Funding	Free From Other Bias	Overall Quality
Kappos 2018[19] **EXPAND**	Yes	Yes	Yes	Yes	Yes	15% lost to follow-up	Yes	Yes	No	Yes	Yes	Good

Table D3. Baseline Characteristics

Reference & Study Name	Arm	N	Age, Years	Female, n (%)	Time Since MS Diagnosis, Years	Time Since Onset of MS Symptoms, Years	Time Since Conversion to SPMS, Years	EDSS Score	Previous DMT Use, n (%)	Relapses Before Screening	Relapse-Free in 2 Years Prior to Study, n (%)	Gadolinium-Enhancing Lesions on T1-Weighted Images
Siponimod												
Kappos 2018[19] EXPAND	Siponimod	1105	Median (range): 49.0 (22-61)	669 (61)	Mean (SD): 12.9 (7.9) Median (range): 12.0 (0.1-44.4)	Mean (SD): 17.1 (8.4) Median (range): 16.4 (1.4-45.0)	Mean (SD): 3.9 (3.6) Median (range): 2.6 (0.1-24.2)	Mean (SD): 5.4 (1.1)	No previous use: 245 (22)	Previous year, mean (SD): 0.2 (0.5) Previous 2 years, mean (SD): 0.7 (1.2)	712 (64)	n (%) – Yes: 237 (21) – No: 833 (75) – Not assessed: 32 (3)
	Placebo	546	Median (range): 49.0 (21-61)	323 (59)	Mean (SD): 12.1 (7.5) Median (range): 11.2 (0.4-39.4)	Mean (SD): 16.2 (8.2) Median (range): 15.4 (1.3-43.0)	Mean (SD): 3.6 (3.3) Median (range): 2.5 (0.1-21.7)	Mean (SD): 5.4 (1.0)	No previous use: 114 (21)	Previous year, mean (SD): 0.3 (0.6) Previous 2 years, mean (SD): 0.7 (1.2)	343 (63)	n (%) – Yes: 114 (21) – No: 415 (76) – Not assessed: 17 (3)
Natalizumab												
Kapoor 2018[30] ASCEND	Natalizumab	439	Mean (SD): 47.3 (7.4)	270 (62)	NR	Mean (SD): 16.8 (7.6)	Mean (SD): 4.7 (3.0)	Median (IQR): 6.0 (5.0-6.5)	NR	Years since most recent relapse, mean (SD): 4.7 (4.1)	312 (71)	Patients with lesions, n/N (%): 114/438 (26%)

Reference & Study Name	Arm	N	Age, Years	Female, n (%)	Time Since MS Diagnosis, Years	Time Since Onset of MS Symptoms, Years	Time Since Conversion to SPMS, Years	EDSS Score	Previous DMT Use, n (%)	Relapses Before Screening	Relapse-Free in 2 Years Prior to Study, n (%)	Gadolinium-Enhancing Lesions on T1-Weighted Images
	Placebo	448	Mean (SD): 47.2 (7.8)	280 (63)	NR	Mean (SD): 16.2 (7.8)	Mean (SD): 4.9 (3.7)	Median (IQR): 6.0 (5.0-6.5)	NR	Years since most recent relapse, mean (SD): 4.8 (4.4)	315 (70)	Patients with lesions, n/N (%): 96/446 (22%)
Beta Interferons												
Kappos 1998[21] EU Trial	Interferon beta-1b	360	Mean (SD): 41.1 (7.2)	209 (58.1)	Time since relapsing risk diagnosis, mean (SD): 8.1 (5.6)	Disease duration, mean (SD): 12.8 (6.6)	Mean (SD): 2.2 (2.4) Time since evidence of progressive deterioration, mean (SD): 3.8 (2.7)	Mean (SD): 5.1 (1.1)	NR	NR	115 (31.9)	NR
	Placebo	358	Mean (SD): 40.9 (7.2)	231 (64.2)	Time since relapsing risk diagnosis, mean (SD): 8.2 (6.1)	Disease duration, mean (SD): 13.4 (7.5)	Mean (SD): 2.1 (2.2) Time since evidence of progressive deterioration, mean (SD): 3.8 (3.4)	Mean (SD): 5.2 (1.1)	NR	NR	101 (28.2)	NR
Panitch 2004[22] N. American	Interferon beta-1b, 160 µg	314	Mean ± SEM: 46.8 ± 0.47	193 (61)	Duration of MS, mean ± SEM: 14.5 ± 0.49		Mean ± SEM: 4.0 ± 0.20	Mean ± SEM: 5.1 ± 0.07	NR	Mean ± SEM: 0.9 ± 0.09	173 (55)	Annual new active lesions, mean ± SEM: 1.0 ± 0.26
	Interferon beta-1b, 250 µg	317	Mean ± SEM: 46.1 ± 0.45	210 (66)	Mean duration of MS ± SEM 14.6 ± 0.44		Mean ± SEM: 4.0 ± 0.19	Mean ± SEM: 5.2 ± 0.06	NR	Mean ± SEM: 0.8 ± 0.06	170 (54)	Annual new active lesions, mean ± SEM: 1.3 ± 0.33

Reference & Study Name	Arm	N	Age, Years	Female, n (%)	Time Since MS Diagnosis, Years	Time Since Onset of MS Symptoms, Years	Time Since Conversion to SPMS, Years	EDSS Score	Previous DMT Use, n (%)	Relapses Before Screening	Relapse-Free in 2 Years Prior to Study, n (%)	Gadolinium-Enhancing Lesions on T1-Weighted Images
	Placebo	308	Mean ± SEM: 47.6 ± 0.46	185 (60)	Duration of MS, mean ± SEM: 14.9 ± 0.48		Mean ± SEM: 4.1 ± 0.20	Mean ± SEM: 5.1 ± 0.07	NR	Mean ± SEM: 0.8 ± 0.07	174 (56)	Annual new active lesions, mean ± SEM: 1.6 ± 0.41
Li 2001[125] SPECTRIMS	Interferon beta-1a, 44 µg	204	Mean (SD) 42.6 (7.3)	137 (67)	Duration of MS, mean (SD): 12.9 (6.9)		Mean (SD): 3.7 (2.7)	Mean (SD): 5.3 (1.1)	NR	In 2 years prior to study, mean (SD): 0.9 (1.3)	106 (52)	NR
	Interferon beta-1a, 22 µg	209	Mean (SD): 43.1 (7.2)	130 (62)	Duration of MS, mean (SD): 13.3 (7.4)		Mean (SD): 4.2 (3.1)	Mean (SD): 5.5 (1.1)	NR	In 2 years prior to study, mean (SD): 0.9 (1.4)	113 (54)	NR
	Placebo	205	Mean (SD): 42.7 (6.8)	123 (60)	Duration of MS, mean (SD): 13.7 (7.2)		Mean (SD): 4.1 (3.2)	Mean (SD): 5.4 (1.1)	NR	In 2 years prior to study, mean (SD): 0.9 (1.2)	107 (52)	NR
Andersen 2004[25] Nordic Trial	Interferon beta-1a, 22 µg	186	Mean (SD): 45.1 (NR)	112 (60)	Duration of MS, mean (SD): 14.2 (NR)		Mean (SD): 4.8 (NR)	Mean (SD): 4.7 (NR)	NR	In 4 years prior to study, mean (SD): 1.7 (NR)	NR (34% relapse-free in prior 4 years)	NR
	Placebo	178	Mean (SD): 46.4 (NR)	107 (60)	Duration of MS (SD): 14.4 (NR)		Mean (SD): 6.1 (NR)	Mean (SD): 5.0 (NR)	NR	In 4 years prior to study, mean (SD): 1.6 (NR)	NR (40% relapse-free in 4 years prior to study)	NR

Reference & Study Name	Arm	N	Age, Years	Female, n (%)	Time Since MS Diagnosis, Years	Time Since Onset of MS Symptoms, Years	Time Since Conversion to SPMS, Years	EDSS Score	Previous DMT Use, n (%)	Relapses Before Screening	Relapse-Free in 2 Years Prior to Study, n (%)	Gadolinium-Enhancing Lesions on T1-Weighted Images
Cohen 2002[26] IMPACT	Interferon beta-1a	217	Mean (SD): 47.2 ± 8.2	138 (64)	Mean (SD): 16.2 ± 9.0	NR	NR	Mean (SD): 5.2 ± 1.1	NR	In year prior to study, mean (SD): 0.6 (1.1) In 3 years prior to study, mean (SD): 1.5 (2.1)	In year prior to study: 129 (59) In 3 years prior to study: 80 (37)	Volume (mm^3), mean (SD): 165.6 (696.5)
	Placebo	219	Mean (SD): 47.9 ± 7.7	141 (64)	Mean (SD): 16.7 ± 9.0	NR	NR	Mean (SD): 5.2 ± 1.1	NR	In year prior to study: 0.5 ± 0.9 In 3 years prior to study: 1.3 ± 2.1	In year prior to study: 135 (62) In 3 years prior to study: 97 (44)	Volume (mm^3), mean (SD): 100.4 (274.5)
Ocrelizumab												
Montalban 2017[33] ORATORIO	Ocrelizumab	488	Median (range): 46.0 (20-56)	237 (48.6)	*Time since PPMS diagnosis* Mean (SD): 2.9 ± 3.2 Median (range): 1.6 (1.1-32.9)	6.7 ± 4.0	NR	Mean (SD): 4.7 ± 1.2	433 (88.7)	NR	NR	Mean (SD): 48.7 ± 38.2

Reference & Study Name	Arm	N	Age, Years	Female, n (%)	Time Since MS Diagnosis, Years	Time Since Onset of MS Symptoms, Years	Time Since Conversion to SPMS, Years	EDSS Score	Previous DMT Use, n (%)	Relapses Before Screening	Relapse-Free in 2 Years Prior to Study, n (%)	Gadolinium-Enhancing Lesions on T1-Weighted Images
	Placebo	244	Median (range): 46.0 (18-56)	124 (50.8)	*Time since PPMS diagnosis* Mean (SD): 2.8 ± 3.3 Median (range): 1.3 (0.1-23.8)	6.1 ± 3.6	NR	Mean (SD): 4.7 ± 1.2	214 (87.7)	NR	NR	Mean (SD): 48.2 ± 39.3
Hauser 2017[32] OPERA I + II (High risk of SPMS subgroup analysis)[34]	Ocrelizumab	175	Age (SD): 40.2 (9.3)	110 (62.9)	Mean (SD): 6.32 (5.7)	Mean (SD): 6.32 (5.7)	NR	Mean (SD): 4.59 (0.6)	Treatment naïve, n (%): 118 (67.4)	Relapses in the last year: 1.33 (0.66) Relapses in the last 2 years: 1.87 (0.94)	NR	Patients, n (%): 65 (37.6)
	Interferon beta-1a	180	Age (SD): 41.5 (8.5)	122 (67.8)	Mean (SD): 6.48 (6.1)	Mean (SD): 10.4 (7.3)	NR	Mean (SD): 4.68 (0.6)	Treatment naïve, n (%): 123 (68.3)	Relapses in the last year: 1.37 (0.81) Relapses in the last 2 years: 1.93 (1.05)	N/A (being relapse free was an exclusion criterion)	Patients, n (%): 61 (34.1)

HR: hazard ratio, IQR: interquartile range, MS: multiple sclerosis, n: number, N: total number, NR: not reported, PPMS: primary-progressive multiple sclerosis, SD: standard deviation, SEM: standard error of the mean, SPMS: secondary-progressive multiple sclerosis

Table D4. Outcomes I

Reference & Study Name	Arm	N	Definition of Confirmed Disability Progression	Confirmed Disability Progression (CDP), n/N (%)	T25FW	MSWS-12	EDSS Score at Endpoint	9HPT
Siponimod								
Kappos 2018[19] EXPAND	Siponimod	1099	1-point increase in EDSS if baseline score was 3.0-5.0, or a 0.5 increase if baseline score was 5.5-6.5.	3 months: 288/1096 (26) 6 months: 218/1096 (20)	Worsening of ≥20% from baseline at 3 months, n/N (%): 432/1087 (40)	Change from baseline, adjusted mean over all visits (95% CI): 2.69 (1.46, 3.92)	NR	NR
	Placebo	546		3 months: 173/545 (32) 6 months: 139/545 (26)	Worsening of ≥20% from baseline at 3 months, n/N (%): 225/543 (41)	Change from baseline, adjusted mean over all visits (95% CI): 4.46 (2.82, 6.10)	NR	NR
	Between-group difference (95% CI), p-value	---		3 months: HR: 0.79 (0.65, 0.95), p=0.013 6 months: HR: 0.74 (0.60, 0.92), p=0.0058	HR: 0.94 (0.80, 1.10), p=0.44	-1.77 (-3.59, 0.05), p=0.057	NR	NR
Natalizumab								
Kapoor 2018[30] ASCEND	Natalizumab	439	Met ≥1 of following score changes from baseline: – ≥1-point increase from baseline EDSS if score was ≤5.5 or ≥0.5-point increase from baseline if EDSS score was ≥6.0 – Increase ≥20% on T25FW	Multicomponent progression: 195/439 (44)	Progression, n/N (%): 153/439 (35) *Responders, n/N (%): 71/383 (19)	Change from baseline to week 96, mean (SD): 2.70 (22.11)	Progression, n/N (%): 69/439 (16)	Progression, n/N (%): 64/439 (15)
	Placebo	449		Multicomponent progression: 214/448 (48)	Progression, n (%): 158/448 (35) *Responders, n (%): 60/363 (17)	Change from baseline to week 96, mean (SD): 4.04 (21.06)	Progression, n/N (%): 67/448 (15)	Progression, n/N (%): 104/448 (23)

Reference & Study Name	Arm	N	Definition of Confirmed Disability Progression	Confirmed Disability Progression (CDP), n/N (%)	T25FW	MSWS-12	EDSS Score at Endpoint	9HPT
	Between-group difference (95% CI), p-value	---	– Increase ≥20% on either hand on 9HPT *Response defined as taking less time to walk 25 feet compared with the shortest time taken pre-dose for ≥75% of the on-treatment T25FW assessments over 96 weeks	Adjusted OR: 0.86 (0.66, 1.13), p=0.287	Adjusted OR: 0.98 (0.74, 1.30), p=0.914 *Responders p=0.437	NR (NR), p=0.541	Adjusted OR: 1.06 (0.74, 1.53), p=0.753	Adjusted OR: 0.56 (0.40, 0.80), p=0.001
Beta Interferons								
Kappos 1998[21] EU Trial	Interferon beta-1b	360	Increase ≥1.0 point of the EDSS confirmed at 3 months, or 0.5 points if baseline EDSS was 6.0 or 6.5 confirmed at 3 months *Note*: EDSS scores were not obtained during relapses unless reported after day 90 of an ongoing relapse	140 (38.9)	NR	NR	EDSS, mean (SD): 5.57 (NR) Change at endpoint¥: 0.47	NR
	Placebo	358		178 (49.7)	NR	NR	EDSS, mean (SD): 5.84 (NR) Change at endpoint¥: 0.60	NR
	Between-group difference 95% CI, p-value	---		NR (NR), p=0.0048	NR	NR	Mean EDSS at endpoint: NR (NR), p=0.0750 Change at endpoint: NR (NR), p=0.0299	NR
Panitch 2004[22] N. American	Interferon beta-1b, 160 µg	314	Time to sustained progression defined as a confirmed 1.0-point increase in EDSS score if baseline score was <6, or 0.5-point increase if EDSS baseline score was 6.0 to 6.5	122 (39)	NR	NR	Mean change from baseline: 0.72	NR
	Interferon beta-1b, 250 µg	317		101 (32)	NR	NR	Mean change from baseline: 0.53	NR
	Placebo	308		105 (34)	NR	NR	Mean change from baseline: 0.62	NR
	Between-group difference 95% CI, p-value	---		All Interferon beta-1b vs. placebo: NR (NR), p=0.640	NR	NR	All Interferon beta-1b vs. placebo: NR (NR), p=0.629	NR

Reference & Study Name	Arm	N	Definition of Confirmed Disability Progression	Confirmed Disability Progression (CDP), n/N (%)	T25FW	MSWS-12	EDSS Score at Endpoint	9HPT
Li 2001[125] SPECTRIMS	Interferon beta-1a 44 µg	204	Increase from baseline by ≥1.0 points if EDSS baseline score <5, or increase from baseline by 0.5 points if baseline EDSS ≥5.5 (confirmed at 3 months)	NR	NR	NR	NR	NR
	Interferon beta-1a 22 µg	209		NR	NR	NR	NR	NR
	Placebo	205		NR	NR	NR	NR	NR
	Between-group difference 95% CI, p-value	---		Combined doses vs. placebo, OR: 0.74 (0.46, 1.20) Time to progression 44 µg vs. placebo, HR: 0.83 (0.65, 1.07), p=0.146	NR	NR	NR	NR
Andersen 2004[25] Nordic Trial	Interferon beta-1a	186	Increase from baseline by ≥1.0 EDSS points; or 0.5 points if baseline EDSS score was ≥5.5, confirmed at 2 consecutive scheduled visits separated by 6 months	77/186 (41)	NR	NR	EDSS at 6 months, mean: 5.35*	NR
	Placebo	178		68/178 (38)	NR	NR	EDSS at 6 months, mean: 5.59*	NR
	Between-group difference 95% CI, p-value	---		HR: 1.13 (0.82, 1.57), p=0.45	NR	NR	NR	NR
Cohen 2002[26] IMPACT	Interferon beta-1a	217	1.0-step increase for baseline EDSS 3.5 to 5.5 and 0.5-step increase for baseline EDSS 6.0 to 6.5 sustained for 3 months	186/217 (85.7)	Seconds, mean (SD): 29.0 (47.0) Seconds, median (range): 10.4 (7.1 – 22.1) Change from baseline to month 24, mean (SD): -0.979 (2.62)	NR	Change from baseline to month 24, mean: 0.258	Mean (SD): 31.1 (16.1) Median (range): 26.4 (23.0 – 32.8) Change from baseline to month 24, mean (SD): -0.202 (0.476)

Reference & Study Name	Arm	N	Definition of Confirmed Disability Progression	Confirmed Disability Progression (CDP), n/N (%)	T25FW	MSWS-12	EDSS Score at Endpoint	9HPT
	Placebo	219		193/219 (88.1)	Seconds, mean (SD): 32.0 (53.0) Seconds, median (range): 11.9 (7.3 – 27.1) Change from baseline to month 24, mean (SD): -1.191 (3.13)	NR	Change from baseline to month 24, mean: 0.272	Mean (SD): 33.2 (30.0) Median (range): 27.5 (23.2 – 34. 8) Change from baseline to month 24, mean (SD): -0.290 (0.494)
	Between-group difference 95% CI, p-value	---		HR: 0.977 (0.679, 1.407), p=0.90	NR (NR), p=0.378	NR	NR (NR), p=0.362	NR (NR), p=0.024
Ocrelizumab								
Montalban 2017[33] ORATORIO	Ocrelizumab	488	Progression sustained for ≥ 12 weeks or ≥24 weeks respectively	At 12 weeks: 160/487 (32.9) At 24 weeks: 144/487 (29.6)	Change in performance from baseline to week 120, mean %: 38.9 Progression ≥20%, n (%): – 12 weeks: 238 (48.8) – 24 weeks: 202 (41.4)	NR	NR	Progression ≥20%, n (%): – Week 12: 83 (17.0) – Week 24: 69 (14.1)
	Placebo	244		At 12 weeks: 96/244 (39.3) At 24 weeks: 87/244 (35.7)	Change in performance from baseline to week 120, mean %: 55.1 Progression ≥20%, n (%): – Week 12: 145 (59.4) – Week 24: 127 (52.0)	NR	NR	Progression ≥20%, n (%): – Week 12: 66 (27.0) – Week 24: 57 (23.4)

Reference & Study Name	Arm	N	Definition of Confirmed Disability Progression	Confirmed Disability Progression (CDP), n/N (%)	T25FW	MSWS-12	EDSS Score at Endpoint	9HPT
	Between-group difference 95% CI, p-value	---		At 12 weeks: HR: 0.76 (0.59, 0.98), p=0.03 At 24 weeks: HR: 0.75 (0.58, 0.98), p=0.04	Relative difference: 29.3 (-1.6, 51.5), p=0.04 Progression at 12 weeks, HR: 0.75 (0.61, 0.92), p=0.005 Progression at 24 weeks, HR: 0.73 (0.59, 0.91), p=0.006	NR	NR	Week 12: HR: 0.56 (0.41 – 0.78), p<0.001 Week 24: HR: 0.55 (0.38 – 0.77), p<0.001
Hauser 2017[32] OPERA I + II (High risk of SPMS subgroup analysis)[34]	Ocrelizumab	175	Increase from baseline EDSS score of at least 1.0 point (or 0.5 points if baseline EDSS score is >5.5), sustained for at least 12 weeks	12 weeks: 6/175 (3.7) 24 weeks: 6/175 (3.7)	12 weeks: 27/175 (15.5) 24 weeks: 23/175 (13.4)	NR	NR	12 weeks, n/N (%): 6/175 (3.8) 24 weeks, n/N (%): 5/175 (3.2)
	Interferon beta-1a	180		12 weeks: 16/180 (8.9) 24 weeks: 13/180 (7.5)	12 weeks: 40/180 (22.6) 24 weeks: 34/180 (19.2)	NR	NR	12 weeks, n/N (%): 15/180 (8.5) 24 weeks, n/N (%): 12/180 (7.1)
	Between-group difference 95% CI, p-value	---		12 weeks, HR: 0.45 (0.18–1.09), p=0.071 24 weeks, HR: 0.54 (0.21–1.35), p=0.2	12 weeks, HR: 0.65 (0.38–1.11), p=0.1 24 weeks, HR: 0.70 (0.39–1.24), p=0.2	NR	NR	12 weeks, HR: 0.46 (0.17–1.23), p=0.1 24 weeks, HR: 0.47 (0.16‑1.37), p=0.2

9HTP: 9-Hole Peg Test, CI: confidence interval, EDSS: Expanded Disability Status Scale, HR: hazard ratio, n: number, N: total number, NR: not reported, OR: odds ratio, T25WT: Timed 25-Foot Walk Test, UTI: urinary tract infection.

¥: Endpoint – Baseline

Table D5. Outcomes II

Reference & Study Name	Arm	N	Confirmed Relapse, n/N (%)	Annualized Relapse Rate, Mean (95% CI)	% Brain Volume Change From Baseline	Patients With No New or Enlarging Lesions on T2-Weighted Images, n/N (%)	Patients With No Gadolinium-Enhancing Lesions on T1-Weighted MRI on All Post-Baseline Scans, n/N (%)
Siponimod							
Kappos 2018[19] EXPAND	Siponimod	1099	113/1061 (11)	0.07 (0.06, 0.09)	Change from month 12 to month 24, % (95% CI): -0.50 (-0.55, -0.44)	584/1026 (57)	917/1026 (89)
	Placebo	546	100/528 (19)	0.16 (0.12, 0.21)	Change from month 12 to month 24, % (95% CI): -0.65 (-0.72, -0.58)	190/510 (37)	341/510 (67)
	Between-group difference (95% CI), p-value	---	HR: 0.54 (0.41-0.70), p<0.0001	RR: 0.45 (0.34, 0.59), p<0.0001	0.15% (0.07, 0.23), p=0.0002	NR	NR
Natalizumab							
Kapoor 2018[30] ASCEND	Natalizumab	439	TAE: 73/439 (17)	0.08 (0.06, 0.10)	Change from week 24 to week 96, mean (SD): -0.66 (0.60)	NR	NR
	Placebo	449	TAE: 122/449 (27)	0.17 (0.14, 0.21)	Change from week 24 to week 96, mean (SD): -0.72 (0.66)	NR	NR
	Between-group difference (95% CI), p-value	---	NR	NR (NR), p<0.001	NR (NR), p=0.242	NR	NR
Beta Interferons							
Kappos 1998[21,80] EU Trial	Interferon beta-1b	360	194 (41.8)	– Overall: 0.44 – Year 1: 0.57 – Year 2: 0.35 – Year 3: 0.24	Change at 36 months, mean (SD): -2.91 (3.11)	NR	NR
	Placebo	358	224 (52.2)	– Overall: 0.64 – Year 1: 0.82 – Year 2: 0.47 – Year 3: 0.35	Change at 36 months, mean (SD): -3.86 (3.53)	NR	NR

Reference & Study Name	Arm	N	Confirmed Relapse, n/N (%)	Annualized Relapse Rate, Mean (95% CI)	% Brain Volume Change From Baseline	Patients With No New or Enlarging Lesions on T2-Weighted Images, n/N (%)	Patients With No Gadolinium-Enhancing Lesions on T1-Weighted MRI on All Post-Baseline Scans, n/N (%)
	Between-group difference (95% CI), p-value	---	Relative difference: -19.9%	– Overall: NR (NR), p= 0.0002 – Year 1: NR (NR), p=0.0095 – Year 2: NR (NR), p=0.0201 – Year 3: NR (NR), p=0.1624	NR (NR), p=0.3434	NR	NR
Panitch 2004[22] N. American	Interferon beta-1b (160 µg)	314	105/314 (33)	0.20 (NR)	NR	NR	NR
	Interferon beta-1b (250 µg)	317	91/317 (29)	0.16 (NR)	NR	NR	NR
	Placebo	308	116/308 (38)	0.28 (NR)	NR	NR	NR
	Between-group difference (95% CI) p-value	---	NR	All Interferon beta-1b vs. placebo: NR (NR), p=0.014	NR	NR	NR
SPECTRIMS 2001[24,125] SPECTRIMS	Interferon beta-1a (44 µg)	204	NR	0.50 (0.45, 0.56)	NR	81/199 (41)	NR
	Interferon beta-1a (22 µg)	209	NR	0.50 (0.44, 0.56)	NR	73/205 (36)	NR
	Placebo	205	NR	0.71 (0.65, 0.78)	NR	48/200 (24)	NR
	Between-group difference 95% CI p-value	---	NR	44 µg vs. Placebo: RR: 0.69 (0.56, 0.85), p<0.001 22 µg vs. Placebo: RR: 0.69 (0.56, 0.84), p<0.001	NR	44 µg vs Placebo: NR (NR), p<0.001 22 µg vs Placebo: NR (NR), p<0.05	NR
Andersen 2004[25] Nordic Trial	Interferon beta-1a (22 µg)	186	Relapse-free at end of study: 114/186 (61)	0.25 (NR)	NR	NR	NR
	Placebo	178	Relapse-free at end of study: 110/178 (62)	0.27 (NR)	NR	NR	NR
	Between-group difference	---	OR: 1.03 (0.67, 1.58),	Rate ratio: 0.90 (0.64, 1.27),	NR	NR	NR

Reference & Study Name	Arm	N	Confirmed Relapse, n/N (%)	Annualized Relapse Rate, Mean (95% CI)	% Brain Volume Change From Baseline	Patients With No New or Enlarging Lesions on T2-Weighted Images, n/N (%)	Patients With No Gadolinium-Enhancing Lesions on T1-Weighted MRI on All Post-Baseline Scans, n/N (%)
	95% CI p-value		p=0.89	p=0.55			
Cohen 2002[26] IMPACT	Interferon beta-1a	217	Relapse free, n (%): 160 (74)	0.20	NR	At 12 months: 147 (77) At 24 months: 111 (63)	NR
	Placebo	219	Relapse free, n (%): 139 (63)	0.30	NR	At 12 months: 113 (58) At 24 months: 75 (42)	NR
	Between-group difference 95% CI p-value	---	NR (NR), p=0.023	NR (NR), p=0.008	NR	Mean reduction in lesions from baseline at month 12: 52.9% Mean reduction in lesions from baseline at month 24: 45.6%	NR
Ocrelizumab							
Montalban 2017[33] ORATORIO	Ocrelizumab	488	NR	NR	-0.90 (-1.00, -0.80)	NR	NR
	Placebo	244	NR	NR	-1.09 (-1.24, -0.95)	NR	NR
	Between-group difference, 95% CI, p-value	---	NR	NR	HR: 17.5 (3.2, 29.3), p=0.02	NR	NR
Hauser 2017[32] OPERA I + II (ITT population)	Ocrelizumab	827	NR	OPERA I: 0.16 (0.12, 0.20) OPERA II: 0.16 (0.12, 0.20)	(change from week 24 to week 96) OPERA I: -0.57 (-0.66, -0.49) OPERA II: -0.64 (-0.73, -0.54)	OPERA I: 157/410 (38.3) OPERA II: 163/417 (39.1)	NR
	Interferon beta-1a	829	NR	OPERA I: 0.29 (0.24, 0.36) OPERA II: 0.29 (0.23, 0.36)	(change from week 24 to week 96) OPERA I: -0.74 (-0.83, -0.65) OPERA II: -0.75 (-0.85, -0.65)	OPERA I: 251/411 (61.3) OPERA II: 259/418 (62.0)	NR
	Between-group difference 95% CI,	---	NR	OPERA I, RR: 0.54 (0.40, 0.72), p<0.001	OPERA I, Difference in rate of brain-volume loss, %: 22.8, p=0.004	OPERA I RR: 0.43 (0.33, 0.56), p<0.001	NR

Reference & Study Name	Arm	N	Confirmed Relapse, n/N (%)	Annualized Relapse Rate, Mean (95% CI)	% Brain Volume Change From Baseline	Patients With No New or Enlarging Lesions on T2-Weighted Images, n/N (%)	Patients With No Gadolinium-Enhancing Lesions on T1-Weighted MRI on All Post-Baseline Scans, n/N (%)
	p-value			OPERA II, RR: 0.53 (0.40, 0.71), p<0.001	OPERA II, Difference in rate of brain-volume loss, %: 14.9, p=0.09	OPERA II RR: 0.36 (0.27, 0.47), p<0.001	

RR: risk ratio, SD: standard deviation, ITT: intention to treat, n: number, N: total number

*no. of subjects (% of total available scans)

Table D6. Harms

Reference & Study Name	Arm	N	Any AE, n (%)	SAE, n (%)	AE Leading to Discontinuation, n (%)	Death, n (%)	Cardiovascular AEs, n (%)	Liver-Related AEs, n (%)	Infections & Infestations, n (%)	Other AEs, n (%)
Siponimod										
Kappos 2018[19] EXPAND	Siponimod	1099	975 (89)	197 (18)	84 (8)	4 (<1)	Bradycardia: 48 (4), Bradyarrhythmia: 29 (3), Hypertension: 137 (12)	Liver-related investigations: 135 (12), ALT increased: 10 (1), AST increased: 5 (<1)	Infections & Infestations: 539 (49), Herpes viral infections: 53 (5)	Peripheral edema: 50 (5)
	Placebo	546	445 (82)	83 (15)	28 (5)	4 (<1)	Bradycardia: 14 (3), Bradyarrhythmia: 2 (0.4), Hypertension: 50 (9)	Liver-related investigations: 21 (4), ALT increased: 2 (<1), AST increased: 1 (<1)	Infections & Infestations: 268 (49), Herpes viral infections: 15 (3)	Peripheral edema: 13 (2)
Natalizumab										
Kapoor 2018[30] ASCEND	Natalizumab	439	401 (91)	90 (20)	21 (4.8)	2 (<1) *Unrelated to study treatment*	Acute myocardial infarction: 1 (<1), Atrial fibrillation: 0	NR	Upper respiratory tract infection: 48 (11), UTI: 102 (23), Urosepsis: 3 (<1), Pneumonia: 2 (<1), PML: 0	NR
	Placebo	449	410 (91)	100 (22)	21 (4.7)	0	Acute myocardial infarction: 2 (<1), Atrial fibrillation: 2 (<1)	NR	Upper respiratory tract infection: 30 (7), Urosepsis: 1 (<1), UTI: 107 (24), Pneumonia: 5 (1), PML: 0	NR
Beta Interferons										
Kappos 1998[21] EU trial	Interferon beta-1b	360	NR	NR	45 (12.5)	3 (0.8) *1 suicide, 1 cardiac arrest, 1 pulmonary embolism*	Hypertension: 14 (3.9)	"higher proportions of patients with abnormal values of liver enzymes"	NR	Leukopenia: 36 (10), Flu syndrome: 213 (59.2), Fever: 142 (39.4), Chills: 79 (21.9), Injection site reaction: 157 (43.6), Rash: 77 (21.4)

Reference & Study Name	Arm	N	Any AE, n (%)	SAE, n (%)	AE Leading to Discontinuation, n (%)	Death, n (%)	Cardiovascular AEs, n (%)	Liver-Related AEs, n (%)	Infections & Infestations, n (%)	Other AEs, n (%)
	Placebo	358	NR	NR	4 (1.1)	1 (0.3) *1 suicide*	Hypertension: 3 (0.8)	NR	NR	Leukopenia: 18 (5.0), Flu syndrome: 133 (37.2), Fever: 47 (13.1), Chills: 26 (7.3), Injection site reaction: 37 (10.3), Rash: 38 (10.6)
Panitch 2004[22] N. American	Interferon beta-1b 160 µg	314	NR	NR	10%	7 *none related to treatment*	NR	ALT increased: 15 (4.8) AST icreased: 8 (2.5)	NR	Leukopenia: 75 (24), Flu syndrome: 141 (45), Chills: 69 (22), Injection site reaction: 173 (55), Headache 182 (58)
	Interferon beta-1b 250 µg	317	NR	NR	9%		NR	ALT increased: 14 (4.4) AST increased: 7 (2.2)	NR	Leukopenia: 78 (25), Flu syndrome: 137 (43), Chills 70 (22), Injection site reaction: 165 (52), Headache: 174 (55)
	Placebo	308	NR	NR	4%		NR	ALT increased: 5 (1.6) AST increased: 3 (1.0)	NR	Leukopenia: 25 (8), Flu syndrome: 102 (33), Chills: 36 (12), Injection site reaction 43 (14), Headache 141 (46)
Li 2001[125] SPECTRIMS	Interferon beta-1a 44 µg	204	NR	NR	7 (3.4)	2 (1.0) *1 suicide; 1 intracerebral hemorrhage*	NR	ALT increased: 47 (23) AST increased: 27 (13)	NR	Flu-like symptoms: 102 (50), Application site disorders: 177 (87), Leukopenia: 43 (21), Lymphopenia: 53 (26)
	Interferon beta-1a 22 µg	209	NR	NR	8 (3.8)	1 (0.5) *1 suicide*	NR	ALT increased: 44 (21) AST increased: 25 (12)	NR	Flu-like symptoms: 107 (51), Application site disorders: 169 (81), Leukopenia: 23 (11), Lymphopenia: 46 (22)
	Placebo	205	NR	NR	3 (1.5)	2 (1.0) *1 presumed subarachnoid hemorrhage; 1 suicide*	NR	ALT increased: 14 (7) AST increased: 6 (3)	NR	Flu-like symptoms: 107 (52), Application site disorders: 84 (41), Leukopenia: 10 (5), Lymphopenia: 31 (15)

Reference & Study Name	Arm	N	Any AE, n (%)	SAE, n (%)	AE Leading to Discontinuation, n (%)	Death, n (%)	Cardiovascular AEs, n (%)	Liver-Related AEs, n (%)	Infections & Infestations, n (%)	Other AEs, n (%)
Andersen 2004[25] Nordic Trial	Interferon beta-1a 22 µg	186	NR	51 (27.4)	16 (8.6)	2 (1.1)	NR	Elevation of liver enzymes (ALT, AST, or abnormal hepatic function): 3 (1.6) ALT increased (lab abnormality): 89 (48)	NR	Flu like symptoms: 69 (37), Headache: 67 (36), Injection site inflammation: 58 (31), Injection site reaction: 50 (27), Depression: 37 (20), Fatigue: 35 (19), Myalgia: 28 (15), Fever: 19 (10), Lymphopenia AE/lab abnormality: 1 (2)/101 (54)
	Placebo	178	NR	49 (27.5)	6 (3.4)	2 (1.1)	NR	Elevation of liver enzymes (ALT, AST, or abnormal hepatic function): 0 ALT increased (lab abnormality): 58 (33)	NR	Flu like symptoms: 39 (22), Headache: 36 (20), Injection site inflammation: 7 (4), Injection site reaction: 14 (8), Depression: 25 (14), Fatigue: 23 (13), Myalgia: 14 (8), Fever: 7 (4), Lymphopenia AE/lab abnormality: 4 (2)/76 (43)
Cohen 2002[26] IMPACT	Interferon beta-1a	217	215	NR	5 (AE related); 8 (AE related) post-follow-up	2	NR	NR	Ecchymosis at injection site: 34 (16), UTI: 53 (35)	Peripheral edema: 28 (13)
	Placebo	218	215	NR	4 (AE related + post-follow-up)	0	NR	NR	Ecchymosis at injection site: 40 (20), UTI: 45 (21)	Peripheral edema: 32 (15)
Ocrelizumab										
Montalban 2017[33] ORATORIO	Ocrelizumab	486	462 (95.1)	99 (20.4)	20 (4.1)	4 (0.8)	NR	NR	Infection: 71.4, UTI: 19.8	Nasopharyngitis: 22.6, Influenza: 11.5
	Placebo	239	215 (90)	53 (22.2)	8 (3.3)	1 (0.4)	NR	NR	Infection: 69.9, UTI: 26.6	Nasopharyngitis: 27.2, Influenza: 8.8

Reference & Study Name	Arm	N	Any AE, n (%)	SAE, n (%)	AE Leading to Discontinuation, n (%)	Death, n (%)	Cardiovascular AEs, n (%)	Liver-Related AEs, n (%)	Infections & Infestations, n (%)	Other AEs, n (%)
Hauser 2017[32] OPERA I + II (ITT population)	Ocrelizumab	827	OPERA I: 327 (80.1) OPERA II: 360 (86.3)	OPERA I: 28 (6.9) OPERA II: 29 (7.0)	OPERA I: 13 (3.2) OPERA II: 16 (3.8)	OPERA I: 0 OPERA II: 1 (0.2)	NR	NR	OPERA I: 231 (56.6) OPERA II: 251 (60.2)	Neoplasm: – OPERA I: 3 (0.7) – OPERA II: 1 (0.2)
	Interferon beta-1a	829	OPERA I: 331 (80.9) OPERA II: 357 (85.6)	OPERA I: 32 (7.8) OPERA II: 40 (9.6)	OPERA I: 26 (6.4) OPERA II: 25 (6.0)	OPERA I: 1 (0.2) OPERA II: 1 (0.2)	NR	NR	OPERA I: 216 (52.8) OPERA II: 217 (52.0)	Neoplasm: – OPERA I: 1 (0.2) – OPERA II: 1 (0.2)

AE: adverse event, ALT: alanine aminotransferase, AST: aspartate aminotransferase, SAE: serious adverse event

Table D7. Siponimod in Relapsing-Remitting MS

Trial Author & Year of Publication	Study Design and duration of Follow-Up, N	Interventions & Dosing (n) Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes	Harms, n (%)
Selmaj et al., 2013[86] BOLD	Phase 2, multicenter, International Randomized, double-blind, adaptive dose-ranging study Study Duration: 6-months (Extension study: 24-months) [87] N (Siponimod 2 mg + Placebo): 111	*Once daily for 6 months* 1) Siponimod: 2 mg† 2) Placebo	Inclusions: – 18-55 years – RRMS diagnosis – ≥1 relapse within previous year, ≥2 relapses within previous two years, or ≥1 Gd-enhancing lesions on MRI at screening – EDSS 0-5.0 Exclusions: – Relapse or corticosteroid treatment in the 30 days prior to randomization – Active infection, macular oedema, diabetes mellitus, immunosuppression, cancer, heart disease, lung disease, or liver disease	Siponimod (n=49) – Age, mean (SD): 37.4 (8.9) years – Female, n (%): 34 (69) – Time since disease onset, mean (SD): 7.2 (6.8) years – Number of relapses in previous year, mean (SD): 1.3 (0.6) – Number of relapses in previous 2 years: 2.1 (1.0) – EDSS, mean (SD): 2.4 (1.2) – Patients with Gd-enhancing T1-lesions, n (%): 26/48 (54%) – Gd-enhancing T1 lesions/patient, mean (SD): 1.7 (3.4) Placebo (n=62) – Age, mean (SD): 35.4 (8.6) years – Female, n (%): 45 (73) – Time since disease onset, mean (SD): 8.0 (6.6) years – Number of relapses in previous year, mean (SD): 1.3 (0.6) – Number of relapses in previous 2 years: 1.8 (0.7) – EDSS, mean (SD): 2.3 (1.1) – Patients with Gd-enhancing T1-lesions, n (%): 35/61 (57) – Gd-enhancing T1 lesions/patient, mean (SD): 2.2 (3.4)	**At 3 months** New or newly enlarged T2 lesions, n 1) Siponimod (n=45): 0.40 (95% CI: 0.20, 0.81)* 2) Placebo (n=61): 1.47 (95% CI: 0.86, 2.53)* *p=0.0049* New Gd-enhancing lesions, n 1) Siponimod (n=45): 0.40 (95% CI: 0.19, 0.81)* 2) Placebo (n=61): 1.29 (95% CI: 0.72, 2.32)* *p=0.0119* **At 6 months** New or newly enlarged T2 lesions, n 1) Siponimod (n=45): 0.41 (95% CI: 0.19, 0.95)* 2) Placebo (n=45): 2.09 (95% CI: 1.26, 3.49)* *p=0.0012* New Gd-enhancing lesions, n 1) Siponimod (n=45): 0.38 (95% CI: 0.15, 0.92)* 2) Placebo (n=45): 1.65 (95% CI: 0.99, 2.69)* *p=0.0051* Annualized relapse rate 1) Siponimod (n=49): 0.20 (95% CI: 0.08, 0.48)* 2) Placebo (n=45): 0.58 (95% CI: 0.34, 1.00)* *p=0.0408*	Any AE, n (%) 1) Siponimod: 48 (98) 2) Placebo: 36 (80) Any AE leading to discontinuation, n (%) 1) Siponimod: 6 (12) 2) Placebo: 2 (4) Any serious AE, n (%) 1) Siponimod: 4 (8) 2) Placebo: 0 (0) Headache, n (%) 1) Siponimod: 15 (31) 2) Placebo: 4 (9)

* Digitized from study publication and should be interpreted with caution †only reporting on results from the FDA approved dose (2 mg). Outcomes were analyzed using a negative binominal generalized regression model. EDSS: Expanded Disability Status Scale, RRMS: Relapsing-Remitting Multiple Sclerosis.

Appendix E. Comparative Value Supplemental Information

Table E1. Impact Inventory

Sector	Type of Impact (Add additional domains, as relevant)	Included in this Analysis from… Perspective?		Notes on Sources (if quantified), Likely Magnitude & Impact (if not)
		Health Care Sector	Societal	
Formal Health Care Sector				
Health Outcomes	Longevity effects	X	X	Captured by impact on disability progression, with increasing disability linked with mortality
	Health-related quality of life effects	X	X	Disability-related health states tied to utility
	Adverse events	☐	☐	Serious adverse events with siponimod in the EXPAND trial were rare and were not expected to be a major driver of the model
Medical Costs	Paid by third-party payers	X	X	Includes treatment cost and direct healthcare cost due to MS
	Paid by patients out-of-pocket	☐	☐	Would reduce the cost of siponimod from the payer perspective, with magnitude depending on average patient cost share
	Future related medical costs	X	X	Lifetime time horizon considers direct healthcare cost due to MS during and after treatment
	Future unrelated medical costs	☐	☐	Not included. Unrelated medical costs are assumed to be equal for siponimod and best supportive care
Informal Health Care Sector				
Health-Related Costs	Patient time costs	NA	☐	As siponimod is orally administered, patient time is expected to have minimal impact on model results
	Unpaid caregiver-time costs	NA	☐	If data were available for caregiver time costs, the

				impact of inclusion in the model is expected to be small to moderate
	Transportation costs	NA	☐	As siponimod is orally administered, transportation time is expected to have minimal impact on model results
Non-Health Care Sectors				
Productivity	Labor market earnings lost	NA	X	Captured by indirect costs included within the model
	Cost of unpaid lost productivity due to illness	NA	X	Captured by indirect costs included within the model
	Cost of uncompensated household production	NA	☐	If data were available for uncompensated household production, the impact of inclusion in the model is expected to be small to moderate
Consumption	Future consumption unrelated to health	NA	☐	Not anticipated to have a significant impact on model results
Social Services	Cost of social services as part of intervention	NA	☐	Not anticipated to have a significant impact on model results
Legal/Criminal Justice	Number of crimes related to intervention	NA	☐	Not anticipated to have a significant impact on model results
	Cost of crimes related to intervention	NA	☐	Not anticipated to have a significant impact on model results
Education	Impact of intervention on educational achievement of population	NA	☐	Not anticipated to have a significant impact on model results
Housing	Cost of home improvements, remediation	NA	☐	If data were available for cost of home improvements, the impact of inclusion in the model is expected to be small to moderate
Environment	Production of toxic waste pollution by intervention	NA	☐	Not anticipated to have a significant impact on model results

NA: not applicable

Adapted from Sanders et al.[126]

Table E2. Undiscounted Results for the Base-Case for Siponimod Compared to BSC

Regimen	Drug Cost	Other Direct Costs	LYs	Ambulatory LYs	QALYs
Overall SPMS Population					
Siponimod	$1,147,873	$391,745	20.3	5.95	4.02
BSC	$0	$398,314	19.9	5.03	3.01
Active SPMS Population					
Siponimod	$482,416	$422,307	20.3	6.66	2.60
BSC	$0	$430,339	19.9	5.03	1.41

BSC: best supportive care, LY: life year, QALY: quality-adjusted life year, SPMS: secondary progressive multiple sclerosis.

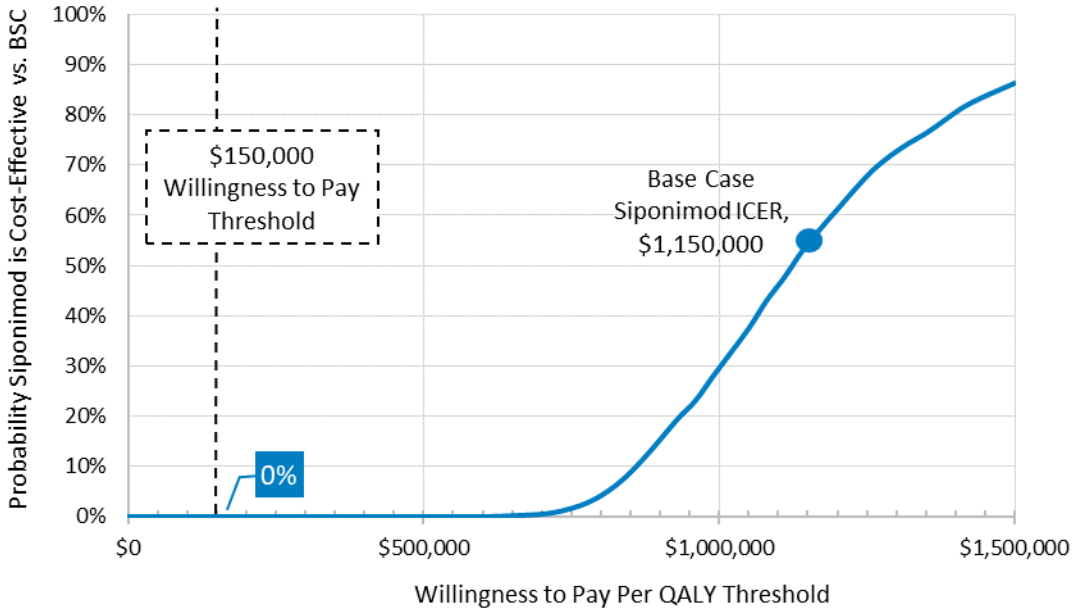
Table E3. Results of Scenario Analyses

Scenario	Cost per Additional LY	Cost per LY of Ambulation	Cost per Additional QALY
Modified societal perspective including indirect costs	$3,730,000	$1,211,000	$1,138,000
Inclusion of caregiver burden	$3,760,000	$1,218,000	$1,219,000
Discontinuation of siponimod at EDSS 8 in the subpopulation with active SPMS	$1,750,000	$472,000	$471,000
Discontinuation of siponimod at EDSS 9 in the subpopulation with active SPMS	$2,300,000	$620,000	$557,000
Relative risk of disability progression for siponimod based on 6-month timepoint of the EXPAND trial	$2,960,000	$948,000	$992,000
Utility values based on Orme 2007	$3,760,000	$1,220,000	$1,080,000
Mortality multipliers by EDSS score from Harding 2018 for EDSS scores 4-9	$1,250,000	$993,000	$1,050,000
Subpopulation with non-active SPMS	$6,360,000	$2,100,000	$3,300,000

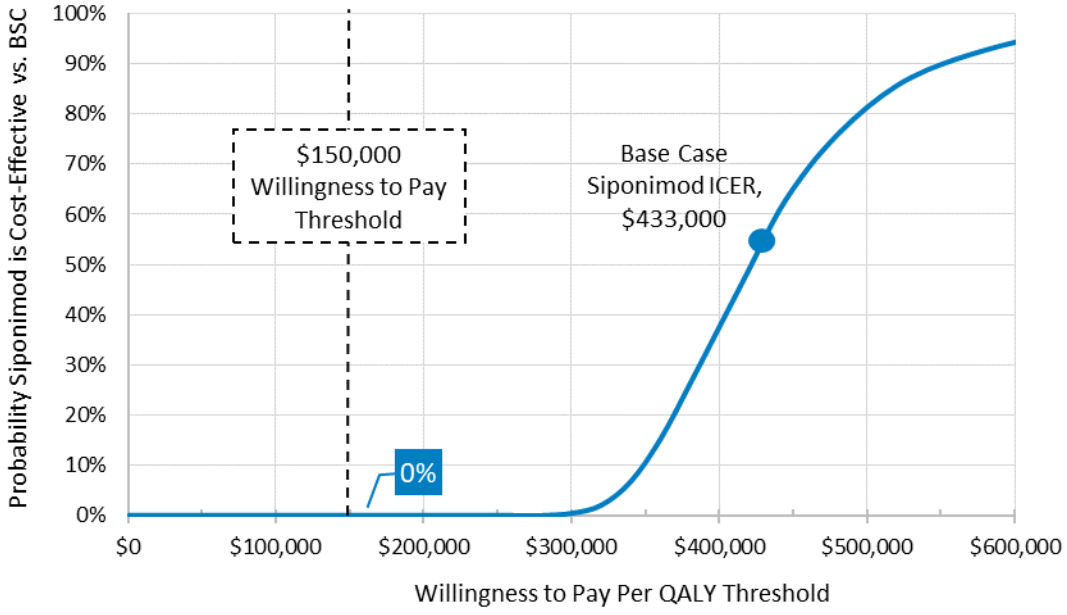
EDSS: Extended Disability Severity Scale, LY: life year, MAIC: matched-adjusted indirect treatment comparison, QALY: quality-adjusted life year, SPMS: secondary progressive multiple sclerosis.

Figure E1. Cost-Effectiveness Acceptability Curve for Siponimod Compared to BSC

Overall SPMS Population



Active SPMS Population



BSC: best supportive care, QALY: quality-adjusted life year

Appendix F. MS Coalition/ICER Survey about Secondary Progressive MS

MS Diagnosis

1) Has your doctor diagnosed you with secondary progressive multiple sclerosis (SPMS)?*

( ) Yes
( ) No
( ) My doctor suspects I may be transitioning to SPMS, but has not yet confirmed the diagnosis
( ) I am not sure whether I have been diagnosed with SPMS, but I have been diagnosed with MS and I believe that I have SPMS

2) In what year were you diagnosed with MS? If you do not know the exact year, please provide your best estimate.

3) In what year were you diagnosed with SPMS? If you do not know the exact year, please provide your best estimate. If you have not received a diagnosis of SPMS, choose the year in which your MS symptoms started gradually getting worse.

Your Background

4) In what year were you born?

5) How do you identify?

( ) Female
( ) Male
( ) Other
( ) Prefer not to answer

6) What is your ethnicity? Check the option with which you MOST CLOSELY identify.

( ) Hispanic or Latino/a
( ) Not Hispanic or Latino/a
( ) Unknown
( ) Prefer not to answer

7) What is your race? Please select ALL that apply.

[ ] American Indian
[ ] Asian
[ ] Black
[ ] Native Hawaiian/Pacific Islander
[ ] White
[ ] Prefer not to answer
[ ] Unknown

8) In which country do you live?

Employment and Insurance

9) Do you currently have health insurance?

( ) Yes
( ) No
( ) Not sure

10) What type(s) of health insurance do you have? Please check all that apply.

[ ] Any private, commercial or pre-paid health plan (such as Aetna, BC/BS, Prudential, Oxford, COBRA, Kaiser, any other HMO or PPO)
[ ] Medicare
[ ] Other Medicare plans (e.g., Medicare Advantage)
[ ] Medicaid
[ ] Tri-Care (formerly CHAMPUS, CHAMP-VA)
[ ] Department of Veterans Affairs OR Canadian Forces
[ ] Indian Health Service OR Non-Insured Health Benefits for First Nations, Inuit
[ ] Universal Health Care - Canadian
[ ] Supplemental insurance (such as Medigap, Value Benefit Plans, AARP, etc.)
[ ] Other primary insurance (please specify):
_____
[ ] Not sure

11) What is your employment status?

( ) I work at least 20 hours per week
( ) I work less than 20 hours per week
( ) I am unemployed but able to work
( ) I am disabled and cannot work
( ) I am retired
( ) I am a student

( ) I am a homemaker

12) Do your MS symptoms and/or treatment limit your ability to work? Please specify approximately how many days of work you missed in the last 12 months due to your disease.

( ) 1-5 days
( ) 6-10 days
( ) 11-15 days
( ) 16-20 days
( ) 21 or more days
( ) I have not missed work in the last 12 months due to my symptoms and/or treatment

Health and Quality of Life

13) Do you require the assistance of a caregiver for any of the following activities? Please check all that apply.

[ ] Personal care (bathing, dressing, etc.)
[ ] House cleaning
[ ] Cooking
[ ] Transportation/mobility
[ ] I do not require assistance to carry out these activities

14) Who is your primary caregiver?

( ) Spouse/partner
( ) Parent
( ) Adult child
( ) Sibling
( ) Friend
( ) Health care aide
( ) Other: _____

15) Please specify approximately how many days of work your primary caregiver missed in the last 12 months due to your symptoms and/or treatment.

( ) 1-5 days
( ) 6-10 days
( ) 11-15 days
( ) 16-20 days
( ) 21 or more days
( ) They have not missed work in the last 12 months due to my symptoms and/or treatment.

( ) They do not work

16) Do you use a mobility aid (e.g., cane, scooter) some or all of the time?

17) Please check the mobility aids you currently use at least some of the time.

[ ] Cane/crutches
[ ] Walker
[ ] Scooter
[ ] Wheelchair
[ ] Other - Write In: _____

18) How often do you use your mobility aids?

( ) 1-3 days a week
( ) 4-6 days a week
( ) Every day

19) How much do you agree with the following statements about having secondary progressive MS?

	Strongly disagree	**Disagree**	**Somewhat agree**	**Agree**	**Strongly agree**
There are fewer treatment options available for me now that I have a progressive form of MS.	( )	( )	( )	( )	( )
My quality of life has declined since my MS started gradually getting worse.	( )	( )	( )	( )	( )
My financial situation has gotten worse since I was diagnosed with secondary progressive MS.	( )	( )	( )	( )	( )
I feel more isolated from friends, family and the community now that my MS has begun to progress.	( )	( )	( )	( )	( )

	Strongly disagree	Disagree	Somewhat agree	Agree	Strongly agree
There are fewer sources of information or help available to me now that I have secondary progressive MS.	( )	( )	( )	( )	( )

20) How does having secondary progressive MS affect your day-to-day life?

21) What effects has your secondary progressive MS had on your family?

MS Treatments

22) Are you currently taking one or more of the following disease modifying therapies (DMTs) for your MS? (Do not include any medications you are using to treat individual symptoms.)

[ ] Aubagio® (teriflunomide)
[ ] Avonex® (Interferon beta-1a)
[ ] Betaseron® (interferon beta-1b)
[ ] Cellcept (mycophenolate mofetil)
[ ] Copaxone® (glatiramer acetate)
[ ] Extavia® (interferon beta-1b)
[ ] Gilenya® (fingolimod)
[ ] Glatopa® (glatiramer acetate)
[ ] Imuran® (azathioprine)
[ ] Lemtrada® (alemtuzumab)
[ ] Novantrone® (mitoxantrone)
[ ] Ocrevus® (ocrelizumab)
[ ] Plegridy® (peginterferon beta-1a)
[ ] Rebif® (interferon beta-1a)
[ ] Rituxan® (rituximab)
[ ] Tecfidera® (dimethyl fumarate)
[ ] Tysabri® (natalizumab)
[ ] Other - Write In: _____
[ ] None of the above

23) Did you begin this treatment before or after your SPMS diagnosis?

( ) Before my SPMS diagnosis
( ) After my SPMS diagnosis

( ) Not sure
( ) Not applicable - I have not received a diagnosis of SPMS

24) Do you believe the drug that you are currently taking for your SPMS is helping your SPMS? Check all that apply.

[ ] Yes, I believe it is helping prevent my SPMS from getting worse.
[ ] Yes, I believe it is helping prevent new MS relapses.
[ ] Yes, I believe it is improving my symptoms.
[ ] I am not sure whether it is helping.
[ ] I do not believe it is helping.

25) How much do you pay out of pocket for your disease-modifying therapy annually?

( ) $0-$500
( ) $501-$1000
( ) $1001-$1500
( ) $1501-$2000
( ) $2001-$2500
( ) More than $2500

26) Why are you not currently taking a disease-modifying therapy? Check all that apply.

[ ] I do not think any of these drugs would help my SPMS.
[ ] My doctor does not recommend that I take any of these drugs.
[ ] My insurance won't cover them as a result of my SPMS diagnosis.
[ ] My insurance does cover them but the out-of-pocket costs are too expensive.
[ ] I am concerned about possible side effects.
[ ] Other - Write In: _____

27) Imagine that a new drug became available specifically for treating secondary progressive MS. How interested would you be in taking this new drug if it could do the following things?

	Not at all interested	**Not very interested**	**Moderately interested**	**Very interested**	**Extremely interested**
It could help me stay at my current mobility level for longer	( )	( )	( )	( )	( )

	Not at all interested	Not very interested	Moderately interested	Very interested	Extremely interested
It could help keep my SPMS symptoms from getting worse	( )	( )	( )	( )	( )
It could help prevent new SPMS symptoms from developing	( )	( )	( )	( )	( )
It could help improve some of my SPMS symptoms	( )	( )	( )	( )	( )
It could help keep me from having new MS relapses	( )	( )	( )	( )	( )
It could help me maintain my current level of activity	( )	( )	( )	( )	( )
It could help me avoid hospitalizations or other significant medical care	( )	( )	( )	( )	( )
It could help prevent brain atrophy (shrinkage)	( )	( )	( )	( )	( )
It is easier to administer than an alternative therapy (i.e. a pill vs. an injection; or an at home treatment vs. doctor's office)	( )	( )	( )	( )	( )

28) Imagine that you started taking a new drug that was available specifically for SPMS. What reasons might prevent you from staying on it? Check all that apply.

[ ] The drug causes side effects such as flu-like symptoms, skin reactions, slow heartbeat, gastrointestinal issues, hair loss, etc.

[ ] There is uncertainty about the long-term risks of the drug (such as liver problems, cancer, infections, thyroid problems, kidney problems, bleeding problems, change in vision, breathing problems, etc.)
[ ] The treatment is expensive
[ ] My health plan makes it difficult to access the drug
[ ] I must visit my doctor each time I need to obtain treatment
[ ] None of these reasons would prevent me from continuing treatment
[ ] Other - Write In: _____

MS Symptoms

29) Have you experienced any of the following since your MS diagnosis? Check all that apply.

[ ] Depression or anxiety
[ ] Fatigue
[ ] Muscle stiffness/tightness (spasticity)
[ ] Problems with thinking or memory (cognition)
[ ] Problems with walking
[ ] Problems with using my hands
[ ] Balance problems
[ ] Urinary or bowel issues
[ ] Vision problems
[ ] Sleep problems
[ ] Pain
[ ] Other - Write In: _____
[ ] None of the above

30) Which symptoms currently interfere with your daily activities?

[ ] Depression or anxiety
[ ] Fatigue
[ ] Muscle stiffness/tightness (spasticity)
[ ] Problems with thinking or memory (cognition)
[ ] Problems with walking
[ ] Problems with using my hands
[ ] Balance problems
[ ] Urinary or bowel issues
[ ] Vision problems
[ ] Sleep problems
[ ] Pain
[ ] Other - Write In: _____

[ ] None of the above

31) Are you currently taking any medications to treat these symptoms, besides a disease-modifying therapy?

32) Please list all of the medications you are taking to treat these symptoms.

33) Overall, do you feel that your symptoms are well-controlled by these medications?

( ) Yes, all of my symptoms are well-controlled
( ) Some of my symptoms are well-controlled but others are not
( ) None of my symptoms are well-controlled
( ) Not sure

34) Are you using any of the following services to help with your MS symptoms? Select all that you are using.

[ ] Physical therapy
[ ] Exercise therapy/coaching
[ ] Occupational therapy
[ ] Speech therapy
[ ] Chiropractic therapy
[ ] Mental health services (psychiatrist, psychologist, other mental health professional)
[ ] Diet/nutrition services
[ ] Wellness services (massage, yoga, acupuncture, etc.)
[ ] Other - Write In: _____
[ ] None of the above

35) What additional support, care, or medications would be most helpful for you to control these symptoms?

Other Comments

36) Is there anything else you'd like us to know?

Appendix G. Public Comments

This section includes summaries of the public comments prepared for the Midwest CEPAC Public Meeting on Thursday, May 23, 2019 in Chicago, IL. These summaries were prepared by those who delivered the public comments at the meeting and are presented in order of delivery. Three speakers did not submit summaries of their public comments.

A video recording of all comments can be found here, beginning at minute 1:16:42. Conflict of interest disclosures are included at the bottom of each statement for each speaker.

Gustavo Suarez Zambrano, MD
Lead Medical Director (Multiple Sclerosis), Novartis

Dr. Suarez Zambrano is a full-time employee of Novartis.

MS is an incurable, progressive neurological disease that affects the quality of life of patients and caregivers. A survey conducted by ICER of approximately 3,000 MS patients reported that patient and caregiver burden is particularly high in SPMS given mobility and cognitive decline, and that patients feel underserved due to a lack of treatment options compared to those who are early in their MS journey.

Siponimod is the first and only oral drug studied and proven effective in active SPMS. Siponimod's approval was based on the largest Phase III clinical trial in SPMS to date. The patients studied were older compared to prior RRMS studies, had a longer duration of disease, and high level of disability. Siponimod showed significant reduction in 3-month confirmed disability progression (primary endpoint) and meaningful improvement in other endpoints such as relapses, MRI, and cognition. Importantly, the ICER report recognizes the relevance of these data in this difficult to treat population, a population in which other current standard of care DMTs have failed to meet their respective primary endpoints.

We appreciate the opportunity to collaborate with ICER on this review. We have provided specific recommendations to ensure an accurate and balanced value assessment of siponimod and maximize the clinical relevance of the report. Most importantly, the assessment should be based on real world clinical practice, and not best supportive care. Novartis is committed to providing safe and efficacious, and innovative treatments for patients, and to support care partners and healthcare providers in all stages of MS.

Jennifer Whiteley, EdD, MSc, MA
HEOR Head of Neuroscience and Rare Diseases in US Medical Affairs, Genentech

Dr. Whiteley is a full-time employee of Genentech.

MS is a progressive disease and there is increasing evidence that disease progression exists throughout the MS spectrum. Early treatment with a therapy that impacts progression, not just relapses, is important for preserving patient function. Patients should have access to efficacious treatments that give them the best chance of maintaining function and independence.

First, we agree with ICER's conclusion that the collective evidence suggests ocrelizumab may potentially benefit SPMS patients. As the first and only treatment approved for both RMS and PPMS, ocrelizumab has demonstrated a consistent effect in decreasing disease activity and delaying disability progression. In an exploratory analysis of an SPMS-like subgroup from OPERA I & II, ocrelizumab reduced the risk of 12-week and 24-week composite progression independent of relapse activity (PIRA) by 40% and 36% respectively, versus an active comparator.

Second, Genentech is committed to leading the science of MS disease progression. We are developing new measures to identify underlying progression that happens in the absence of relapse activity.

Lastly, we encourage ICER to continuously evaluate how it can best incorporate outcomes that are meaningful to patients. Traditional endpoints, developed up to 40-years ago, may not holistically capture changes in progression of symptoms.

In conclusion, Genentech is committed to advancing the science of MS to improve outcomes for patients and generating evidence that demonstrates value to a broad range of stakeholders. We thank ICER for providing the opportunity to comment and the MS community for providing their perspectives and helping advance our understanding and treatment of MS.

Appendix H. Conflict of Interest Disclosures

Tables H1 through H3 contain conflict of interest (COI) disclosures for all participants at the May 23, 2019 Public Meeting of the Midwest CEPAC.

Table H1. ICER Staff and Consultant COI Disclosures

Name	Organization	Disclosures
Ellie Adair, MPA	ICER	*
Lisa Bloudek, PharmD, MS	University of Washington	*
Pamela Bradt, MD, MPH	ICER	*
Josh J. Carlson, PhD, MPH	University of Washington	*
Pamela Bradt, MD, MPH	ICER	*
Noemi Fluetsch, MPH	ICER	*
Maggie O'Grady	ICER	*
Steve Pearson, MD, MSc	ICER	*
David Rind, MD, MSc	ICER	*
Ravi Sharaf, MD, MS	Weill Cornell Medicine	*
Patty Synnott, MALD, MS	ICER	*

* No relevant conflicts of interest to disclose, defined as more than $10,000 in healthcare company stock or more than $5,000 in honoraria or consultancies during the previous year from health care manufacturers or insurers.

Table H2. Midwest CEPAC Panel Member COI Disclosures

Name	Organization	Disclosures
Eric Armbrecht, PhD (Chair)	Saint Louis University Center for Health Outcomes Research	*
Nicolas Bagley, JD	University of Michigan Law School	*
Ryan Barker, MSW, MPPA	Missouri Foundation for Health	*
Bijan Borah, PhD	Mayo Clinic College of Medicine and Science	*
Aaron Carroll, MD, MS	Indiana University School of Medicine	*
Don Casey, MD, MPH, MBA	IPO4Health; Medecision	*
Gregory Curfman, MD	Journal of the American Medical Association (JAMA)	*
Stacie Dusetzina, PhD	Vanderbilt University School of Medicine	*
Elbert Huang, MD, MPH	University of Chicago	*
Jill Johnson, PharmD	University of Arkansas for Medical Sciences	*
Timothy McBride, PhD	Washington University in St. Louis	*
Scott Micek, PharmD	Saint Louis College of Pharmacy	*
Reem Mustafa, MD, MPH, PhD	Saint Louis College of Pharmacy	*
Harold Pollack, PhD	University of Chicago	*
Kurt Vanden Bosch, PharmD	St. Luke's Health System	*
Timothy Wilt, MD, MPH	Minneapolis VA Center for Chronic Disease Outcomes Research	*
Stuart Winston, DO	St. Joseph Mercy Health System	*

* No relevant conflicts of interest to disclose, defined as more than $10,000 in healthcare company stock or more than $5,000 in honoraria or consultancies during the previous year from health care manufacturers or insurers.